Research Article

Cancer Epidemiology, Biomarkers & Prevention

# Prognostic Impact of Comorbidity among Long-Term Breast Cancer Survivors: Results from the LACE Study

Dejana Braithwaite[1], Dan H. Moore[1], William A. Satariano[2], Marilyn L. Kwan[3], Robert A. Hiatt[1], Candyce Kroenke[3], and Bette J. Caan[3]

## Abstract

**Background:** Little is known about the long-term impact of comorbidity among women with breast cancer.

**Methods:** We studied a prospective cohort of 2,272 women with breast cancer, who were recruited following initial breast cancer treatment. Associations of the Charlson comorbidity index (CCI) and hypertension with survival were evaluated in delayed entry Cox proportional hazards models.

**Results:** During a median follow-up of nine years, higher CCI scores were independently associated with an increased risk of death from all causes [HR, 1.32; 95% confidence interval (CI), 1.13–1.54] and from nonbreast cancer causes (HR, 1.55; 95% CI, 1.19–2.02), but not from breast cancer (HR, 1.14; 95% CI, 0.93–1.41). Hypertension was independently associated with an increased risk of death from all causes (HR, 1.55; 95% CI, 1.20–1.99), from nonbreast cancer causes (HR, 1.67; 95% CI, 1.10–2.54), and from breast cancer (HR, 1.47; 95% CI, 1.03–2.09), but these associations were no longer significant after adjustment for antihypertensive medication. The relationship between the CCI and overall survival was the strongest among women with stage I disease (stage I, HR, 1.65; 95% CI, 1.26–2.16 vs. stage III, HR, 0.53; 95% CI, 0.23–1.25).

**Conclusion:** The CCI was independently associated with lower overall and nonbreast cancer survival, but not with breast cancer–specific survival.

**Impact:** Comorbidity may play an important role in breast cancer outcomes. *Cancer Epidemiol Biomarkers Prev; 21(7); 1115–25. ©2012 AACR.*

## Introduction

Although breast cancer, the most common cancer among women in developed countries, aside from nonmelanoma skin cancer, remains one of the leading causes of cancer death, survival has markedly improved in recent decades (1). Principally, 5-year survival rates are close to 90% for women with stage I disease, but considerable variations exist in the length of survival among breast cancer patients (2), even presenting within the same disease stage, and one of the contributing reasons for these variations may be the presence of comorbidity or concurrent chronic conditions in some survivors (3–6). Women with breast cancer, especially those aged 65 and older, often present with one or more comorbid conditions, such as heart disease, diabetes, hypertension, or arthritis, at the time of diagnosis (7–9). Whereas comorbidity has been shown to have short-term effects among women with breast cancer (10), any long-term effects on breast cancer–specific and overall health outcomes are unknown. A better understanding of these relationships may help not only to illuminate predictors of the variability in survival but also to identify opportunities to intervene for improved survival. Specifically, there is a need to identify high-risk populations that could be targeted with interventions to promote quality and lengthy survival (11).

In this study of the long-term prognostic role of comorbidity, we considered death from breast cancer, nonbreast cancer causes, and all causes among women in a population-based cohort of early-stage breast cancer survivors, the Life After Cancer Epidemiology (LACE; ref. 12) study. Women with incident breast cancer were followed for a median of 9 years since diagnosis. By including both middle-aged and elderly women with breast cancer, this large cohort of breast cancer survivors was suitable for examining the long-term consequences of comorbidity following initial breast cancer treatment while taking into account the known prognostic factors in the clinical, lifestyle-related, and sociodemographic domains. We also evaluated the extent to which the effect of comorbidity on long-term survival differed as a function of women's chronologic age and tumor stage at diagnosis.

**Authors' Affiliations:** [1]Department of Epidemiology and Biostatistics and Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco; [2]School of Public Health, University of California, Berkeley; and [3]Kaiser Permanente Northern California, Division of Research, Oakland, California

**Corresponding Author:** Dejana Braithwaite, Department of Epidemiology and Biostatistics, University of California, San Francisco, 185 Berry Street, Suite 5700, San Francisco, CA 94107. Phone: 415-514-8019; Fax: 415-514-8150; E-mail: DBraithwaite@epi.ucsf.edu

**doi:** 10.1158/1055-9965.EPI-11-1228

## Materials and Methods

### Study population

The study population consisted of women diagnosed with stage I (≥1 cm), II, or IIIa breast cancer from 1997 to 2000 in the Kaiser Permanente Northern California Cancer Registry or the Utah Cancer Registry. Eligible women were diagnosed on average 21 months (range 9–39 months) before enrollment, had completed cancer treatment, and were free of any documented recurrence during that period. In addition, women who were eligible but declined participation in the Women's Healthy Eating and Lifestyle (WHEL; ref. 13) study, a dietary intervention trial examining the prevention of breast cancer recurrence, were included. A total of 2,586 (45.7%) completed initial enrollment; subsequent review to confirm eligibility left 2,272 women in the cohort. The large majority of cohort members (82%) came from Kaiser Permanente, 12% from Utah, and 6% from WHEL. The upper age restriction for enrollment to the study was 79 years. This sample comprised the final study population for the present analysis.

The Institutional Review Boards at the University of California, San Francisco, and Kaiser Permanente, Northern California, approved this study.

### Assessment of comorbidity

Women were asked: "Has a doctor or other health professional ever told you that you have any of the following conditions?" and the response was yes/no. Figure 1 shows comorbidities that were used to construct the Charlson comorbidity index (CCI) based on patient interviews. The comorbidity burden was estimated using the interview-based version of the CCI (14), the most common comorbidity index that summarizes many key health conditions (15). Developed among patients admitted to an emergency department with respect to mortality at 1 year of follow-up as a function of comorbidity, the CCI was subsequently validated in a cohort of hypertensive patients (16). Each condition included in the original CCI conferred an independent relative risk of death of 1.2. The comorbid conditions in the original CCI were weighted so that those leading to relative risks between 1.2 and <1.5 were scored as 1; between 1.5 and <2.5 as 2; between 2.5 and <3.5 as 3; and 2 conditions with a relative risk of 6 or more were scored as 6. The total scores calculated by tallying these weighted scores range from 1 to 6 (0 if the comorbidity is absent) are then collapsible into 4 summary categories: 0, 1–2, 3–4, and 5 points.

| CCI Weight | Comorbid conditions |
|---|---|
| 0 | No comorbid conditions |
| 1 | Heart attack (myocardial infarction)<br>Peripheral arterial disease<br>Other diagnosed heart problems<br>Stroke<br>Asthma<br>Ulcer disease<br>Insulin-dependent diabetes<br>Arthritis |
| 2 | Renal disease/kidney stones<br>Diagnosed cancer |
| 3 | Cirrhosis |

Figure 1. Formation of the Charlson comorbidity index. Prevalent comorbid conditions for each subject were assigned weights according to the table. The sum of the weights was then used to form the ordinal Charlson index (Charlson index of 0, no comorbid conditions; Charlson index of 1, sum of weights equal to 1; Charlson index of 2, sum of weights ≥2; ref. 15).

In addition to the CCI, we assessed the independent effects of a common condition that is not included in this index, hypertension. Previous research indicates that hypertension might be independently associated with survival among women with incident breast cancer (17, 18). Women were also asked whether they were receiving medication to manage their hypertension; a binary (yes/no) variable was included in this analysis. All of the aforementioned assessments were carried out at baseline.

### Outcome ascertainment

To monitor outcomes in the LACE cohort, a health status update questionnaire was mailed to participants semi-annually until April 2006 and annually thereafter. The questionnaire asked women about any events that might have occurred in the preceding 6 months (or 12 months on the revised questionnaire), including recurrences or new primary breast cancers, hospitalizations, and other cancers. Nonrespondents to the mailed health status update questionnaire were telephoned and asked about any new events. All reported deaths from any source, including date and cause, were confirmed by death certificate. A research associate (E. Weltzien) categorized information on death certificates as breast cancer death or nonbreast cancer death. Outcome ascertainment was updated regularly by surveillance of electronic outpatient, cancer registry, and mortality files for all participants, including those who dropped out ($n = 90$) or were lost to active follow-up ($n = 15$). In this analysis, the outcomes of interest were survival from nonbreast cancer causes, survival from breast cancer–specific causes, and overall survival.

### Covariates

Covariates in these analyses included sociodemographic, lifestyle-related, and clinical prognostic factors that could potentially confound or modify an association between comorbidity and survival based on the existing literature and a priori hypotheses. The sociodemographic covariates included age (calculated as the difference between date of enrollment and reported date of birth), race/ethnicity, and education, the last 2 being self-reported at baseline. Lifestyle-related factors included smoking status (never, former, and current) and body mass index (BMI) at enrollment [calculated as weight/height ($kg/m^2$) from self-reported weight and height]. Three standard BMI categories (normal weight, <25; overweight, 25–30; and obese, ≥30) were used (19); we also

separately evaluated underweight women (BMI $\leq$ 18.5). Physical activity was assessed in the LACE study with a questionnaire based on the Arizona Activity Frequency Questionnaire (20). Standard metabolic equivalent task (MET) values were assigned to each activity. Frequency was then 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 hours per week (21).

Medical factors were obtained from chart review for both Kaiser and non-Kaiser members. These factors included tumor size, histology, lymph node involvement, and distant metastasis, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2) status, and treatments (type of surgery, radiation, chemotherapy, and use of adjuvant tamoxifen). Stage at diagnosis was classified according to the Tumor, Nodal, Metastasis system based on the criteria of the fifth edition of the American Joint Committee on Cancer (22).

### Statistical analyses

Differences in means and proportions of each potential covariate by the CCI score (i.e., CCI = 0, CCI = 1, CCI $\geq$ 2) were compared using Pearson $\chi^2$ tests for categorical variables. Univariate and multivariable associations between comorbidity and survival were examined using Kaplan–Meier plots and Cox proportional hazards models. Guided by *a priori* considerations (23), separate delayed entry Cox proportional hazards models (24, 25) with time since diagnosis as the time scale were used to estimate the risk of each outcome associated with comorbidity, accounting for varying times of enrollment into the cohort and adjusting for covariates. Risk was expressed as a HR and 95% confidence interval (CI). The type I error was set at 0.05 and all reported $P$ values are 2-sided.

Follow-up time ended at the date of first confirmed date of death, depending on the specific analysis. Individuals who did not die were censored at date of last contact (either most recent questionnaire on health status update or electronic surveillance). When death due to nonbreast cancer causes was analyzed, breast cancer–specific deaths were censored. After computing unadjusted Cox proportional hazards models for comorbidity, known prognostic variables and those that showed statistically significant relations with either the independent or dependent variable were added to the model (if $P < 0.10$ in a model including all other significant predictors). All Cox proportional hazards models were tested for proportionality of hazards using Schoenfeld residuals (26). When this assumption was violated, stratified proportional hazards models were fitted; no material differences in HRs were observed. Multivariable models were stratified by age at diagnosis and tumor stage. When interaction terms were considered, they were entered as the cross-product term of the 2 variables in the interaction. To avoid collinearity in modeling, tamoxifen use and ER status were entered into the same model by creating variables, "ER positive/no tamoxifen" and "ER positive/tamoxifen." Stata version 11.0 software (StataCorp LP) was used to conduct statistical analyses.

## Results

### Characteristics of study participants by comorbidity

We included 2,272 women with breast cancer. The majority of the women were early-stage breast cancer survivors with 80% having stage I or IIa breast cancer at the time of diagnosis (Table 1). The median age was 57 years (SD = 13.2 years; range 21–79 years) at the time of study entry. The sample was ethnically and socioeconomically diverse: 20% of participants were non-white, and nearly 30% had a high school education or less.

A CCI score of $\geq$1 was present in 54% of patients. The proportion of women with a CCI score of $\geq$1 generally increased with age; 18.2% of women with a CCI score of 0 were aged 65 to 79 versus 34.8% of women with a CCI score of 1 and 41.4% of women with a CCI score of $\geq$2 ($P <$ 0.001, Table 1). Women with higher CCI scores were more likely to be overweight or obese; 33.9% women with a CCI score of 2 or more had a BMI of at least 30 and 27.5% women with a CCI score of 1 versus 22.4% of women with a CCI score of 0 ($P <$ .001, Table 1). Women with higher CCI scores were also disproportionately less educated; 31.3% women with a CCI score of $\geq$2 and 26.6% women with a CCI score of 1 had a high school education or less, compared with 24.6% of women with a CCI score of 0 ($P <$ 0.001). In addition, women with a CCI score of $\geq$2 were less physically active compared with women with a CCI score of 0 (MET h/wk: $\geq$46 mean = 435 vs. 218, respectively, $P$ = .006). Furthermore, patients with a CCI score of $\geq$2 were less likely to receive chemotherapy (47.9% vs. 64.9%, respectively, $P <$ 0.001) and radiotherapy (62.6% vs. 66%, respectively, $P$ = .05) than patients with the CCI score of 0. However, there were no significant differences in the proportions of women with more advanced stage and adverse nodal status and ER/PR/HER2 status by comorbidity level. Although proportions of breast cancer death did not differ by women's comorbidity level, more women with CCI scores of $\geq$2 than those with scores of 0 died of nonbreast cancer causes (9.5% vs. 2.7%, respectively, $P <$ .001, Table 1).

In addition, hypertensive women were less likely than normotensive women to receive chemotherapy (45.7% vs. 62.3%, respectively, $P <$ .001) and radiotherapy (57.8% vs. 65.4%, respectively, $P$ = .001), but there were no differences in the receipt of surgery or hormonal therapy by hypertensive status.

### Survival data

The median follow-up in the entire LACE cohort of 2,272 women was 9 years (SD = 1.5 years, range, 1–11 years); 95% of the women were followed for a minimum of 6.3 years. Of the total of 264 deaths, 120 were attributable to nonbreast cancer causes (5% of the cohort) and 164 to breast cancer causes (7% of the cohort).

**Table 1.** Characteristics of the study population by comorbidity based on the CCI

| Characteristics | Total cohort ($n = 2,272$) | CCI = 0 ($n = 1,011$) | CCI = 1 ($n = 599$) | CCI ≥ 2 ($n = 522$) | $P^a$ |
|---|---|---|---|---|---|
| Age at diagnosis, y, no. (%) | | | | | |
| <50 | 551 (24.2) | 355 (35.1) | 110 (18.4) | 74 (14.2) | |
| 50–64 | 1,037 (45.7) | 472 (46.7) | 280 (46.8) | 231 (44.3) | <0.001 |
| 65–79 | 682 (30.0) | 184 (18.2) | 208 (34.8) | 216 41.4) | |
| Education, no. (%) | | | | | |
| ≤4 y high school | 619 (27.4) | 249 (24.6) | 159 (26.6) | 163 (31.3) | |
| College | 842 (37.2) | 367 (36.3) | 240 (40.1) | 192 (36.9) | =0.008 |
| Graduate degree | 800 (35.4) | 394 (39.0) | 199 (33.3) | 165 (31.7) | |
| Race/ethnicity, no. (%) | | | | | |
| White | 1,814 (80.0) | 776 (76.8) | 487 (81.4) | 446 (85.4) | |
| Black | 112 (4.9) | 51 (5.0) | 30 (5.0) | 22 (4.2) | |
| Hispanic | 142 (6.3) | 73 (7.2) | 35 (5.8) | 24 (4.6) | =0.001 |
| Asian | 129 (5.7) | 80 (7.9) | 28 (4.7) | 14 (2.7) | |
| Other | 69 (3.0) | 30 (2.3) | 18 (3.0) | 16 (3.0) | |
| BMI (kg/m$^2$), no. (%) | | | | | |
| <25 | 745 (39.0) | 372 (43.7) | 196 (38.3) | 138 (31.8) | |
| 25–30 | 650 (34.0) | 288 (33.8) | 175 (34.2) | 149 (34.3) | <0.001 |
| >30 | 516 (27.0) | 191 (22.4) | 141 (27.5) | 147 (33.9) | |
| Cigarette smoking, no. (%) | | | | | |
| Never | 1,200 (52.9) | 550 (54.5) | 329 (54.9) | 251 (48.1) | |
| Past | 894 (39.4) | 380 (37.6) | 233 (38.9) | 221 (42.3) | =0.054 |
| Current | 173 (7.6) | 79 (7.8) | 37 (6.18) | 50 (9.6) | |
| Adjuvant tamoxifen, no. (%) | | | | | |
| No | 501 (22.2) | 236 (23.5) | 123 (20.6) | 108 (20.8) | |
| Past | 159 (7.0) | 71 (7.06) | 42 (7.0) | 38 (7.3) | = 0.653 |
| Current | 1,600 (71.0) | 698 (69.4) | 432 (72.3) | 373 (71.9) | |
| Chemotherapy, no. (%) | | | | | |
| No | 974 (42.9) | 355 (35.1) | 261 (43.5) | 272 (52.1) | <0.001 |
| Yes | 1,297 (57.1) | 656 (64.9) | 338 (56.4) | 250 (47.9) | |
| Radiotherapy, no. (%) | | | | | |
| No | 843 (37.1) | 343 (33.9) | 239 (39.9) | 195 (37.3) | =0.049 |
| Yes | 1,429 (63.0) | 668 (66.0) | 360 (60.1) | 327 (62.6) | |
| Surgery[b], no. (%) | | | | | |
| Conserving | 1,148 (50.5) | 529 (52.3) | 297 (49.6) | 262 (50.1) | =0.515 |
| Mastectomy | 1,124 (49.4) | 482 (47.7) | 302 (50.4) | 260 (49.8) | |
| Stage, no. (%) | | | | | |
| I | 1,057 (46.6) | 445 (44.1) | 299 (50.0) | 248 (47.7) | |
| IIA | 762 (33.6) | 365 (36.2) | 182 (30.4) | 168 (32.3) | =0.157 |
| IIB | 376 (16.6) | 173 (17.1) | 95 (15.9) | 87 (16.7) | |
| III | 71 (3.1) | 25 (2.5) | 22 (3.7) | 17 (3.3) | |
| Lymph node positivity, no. (%) | | | | | |
| No | 1,350 (63.1) | 592 (62.3) | 370 (65.2) | 303 (61.8) | =0.425 |
| Yes | 790 (36.9) | 358 (37.7) | 197 (34.7) | 187 (38.1) | |
| ER positivity, no. (%) | | | | | |
| No | 390 (17.3) | 184 (18.3) | 107 (18.0) | 78 (15.2) | =0.325 |
| Yes | 1,852 (82.4) | 816 (81.4) | 487 (82.0) | 433 (84.4) | |
| PR positivity, no. (%) | | | | | |
| No | 668 (29.7) | 308 (30.7) | 174 (29.3) | 145 (28.3) | =0.376 |
| Yes | 1,574 (71.0) | 692 (69.1) | 420 (70.7) | 366 (71.3) | |
| HER2 positivity, no. (%) | | | | | |
| No | 1,642 (74.8) | 724 (73.8) | 444 (76.5) | 374 (75.2) | =0.053 |
| Yes | 318 (14.5) | 161 (16.4) | 74 (12.8) | 59 (11.9) | |

*(Continued on the following page)*

**Table 1.** Characteristics of the study population by comorbidity based on the CCI (Cont'd)

| Characteristics | Total cohort ($n = 2,272$) | CCI = 0 ($n = 1,011$) | CCI = 1 ($n = 599$) | CCI ≥ 2 ($n = 522$) | $P^a$ |
|---|---|---|---|---|---|
| Total physical activity, MET-h/wk, no. and Mean (SD) | 1,811, 52.2 (32.0) | 830, 53.8 (33.5) | 488, 53.2 (32.4) | 493, 48.5 (28.6) | |
| Under 46 | 1,192 (56.7) | 528 (54.8) | 304 (54.1) | 360 (62.3) | =0.006 |
| 46 or more | 911 (43.3) | 435 (45.2) | 258 (45.9) | 218 (37.3) | |
| Breast cancer death, no. (%) | 164 (7.2) | 70 (7.3) | 44 (7.8) | 43 (7.4) | =0.092 |
| Nonbreast cancer death, no. (%) | 120 (5) | 26 (2.7) | 21 (3.7) | 55 (9.5) | <0.001 |

NOTE: Numbers may not equal the total study sample because of missing data.

[a]*P* values were computed using Pearson $\chi^2$ tests for categorical variables.

[b]Breast-conserving surgery included lumpectomy, wide excision, partial mastectomy, segmental mastectomy, or quadrantectomy; mastectomy included modified radical mastectomy (simple mastectomy with lymph node dissection), total mastectomy without axillary lymph node dissection, and radical mastectomy with pectoral muscle dissection.

### Comorbidity and survival

We generated Kaplan–Meier survival curves by the CCI for all-cause survival (Fig. 2A), survival from nonbreast cancer causes (Fig. 2B), and breast cancer–specific survival (Fig. 2C). In addition, we generated Kaplan–Meier plots by hypertension for all-cause survival (Fig. 2D), survival from nonbreast cancer causes (Fig. 2E), and breast cancer–specific survival (Fig. 2F). We also calculated HRs for the effect of the CCI and other non-CCI conditions on nonbreast cancer, breast cancer–specific, and overall survival (Table 2). In a multivariable model that included age, education, race/ethnicity, chemotherapy, radiation, tamoxifen, smoking, physical activity, BMI, tumor stage, hormone receptor status, and nodal status, we found that women with comorbid conditions included in the CCI (i.e., CCI > 0) had a statistically significantly increased risk of death from all causes (HR, 1.32; 95% CI, 1.13–1.54) and from nonbreast cancer causes (HR, 1.55; 95% CI, 1.19–2.02) but not significantly from breast cancer (HR, 1.14; 95% CI, 0.93–1.41; Table 2; Fig. 2).

In addition to the overall CCI, hypertension was independently associated with an increased risk of breast cancer–specific death after adjustment for aforementioned covariates and the CCI (HR, 1.47; 95% CI, 1.03–2.09) as well as with the risk of all-cause death (HR, 1.55; 95% CI, 1.20–1.99) and the risk of death from other causes (HR, 1.67; 95% CI, 1.10–2.54; Table 2). After further adjustment for antihypertensive medication, these estimates remained elevated but were no longer statistically significant (Table 2).

There was a dose–response relationship between the CCI score and overall survival as well as survival from nonbreast cancer causes, but not with breast cancer–specific survival (Table 3).

When modeling the effect of both the CCI and hypertension, the confounders that explained most of the variance in survival in adjusted models included age, tumor stage, smoking status, and education.

### Comorbidity and survival by women's age at breast cancer diagnosis

We examined the possible disproportionate impact of comorbidity on survival by women's age at breast cancer diagnosis (Table 4). Overall, higher CCI scores tended to have a greater adverse effect on overall and on nonbreast cancer survival in younger age groups, after adjustment for other factors. In multivariable models, we found a decreasing trend with age in the association between the CCI and overall survival (HR, 1.49; 95% CI, 0.91–2.43, for age <50; HR, 1.42; 95% CI, 1.12–1.80, for ages 50–64 and HR, 1.17 for ages 65–79, 95% CI, 0.94–1.47) and nonbreast cancer survival (HR, 1.84; 95% CI, 1.11–3.05, for ages 50–64 and HR, 1.29; 95% CI, 0.94–1.78 for ages 65–79). Similarly, in multivariable models, HRs for the association of the CCI with survival from nonbreast cancer causes were higher among women aged 50 to 65 years (HR, 1.84; 95% CI, 1.11–3.05) than among those aged ≥65 (adjusted HR, 1.29; 95% CI, 0.94–1.78). Although adjusted HRs among women aged ≤50 were the highest, CIs were wide in this group (Table 4). We found some evidence of a statistically significant interaction among women aged ≥65 with the CCI = 1 in relation to overall survival (HR, 0.31; 95% CI, 0.10–0.96, $P = .04$).

When we modeled the effect of hypertension, the risk of death generally increased across age strata, but the large CIs in adjusted models, particularly in those further adjusted for antihypertensive medication, rendered these effects statistically nonsignificant (Table 5).

### Comorbidity and survival by tumor stage

To better understand the relationships among comorbidity, extent of disease, and survival, we carried out analyses stratified by tumor stage (Table 4). In fully adjusted models, the effect of the CCI on overall survival was highest for women with stage I disease (HR, 1.65; 95% CI, 1.26–2.16) followed by those with stage IIa disease (HR, 1.33; 95% CI, 1.02–1.74), stage IIb (HR, 1.09; 95% CI,

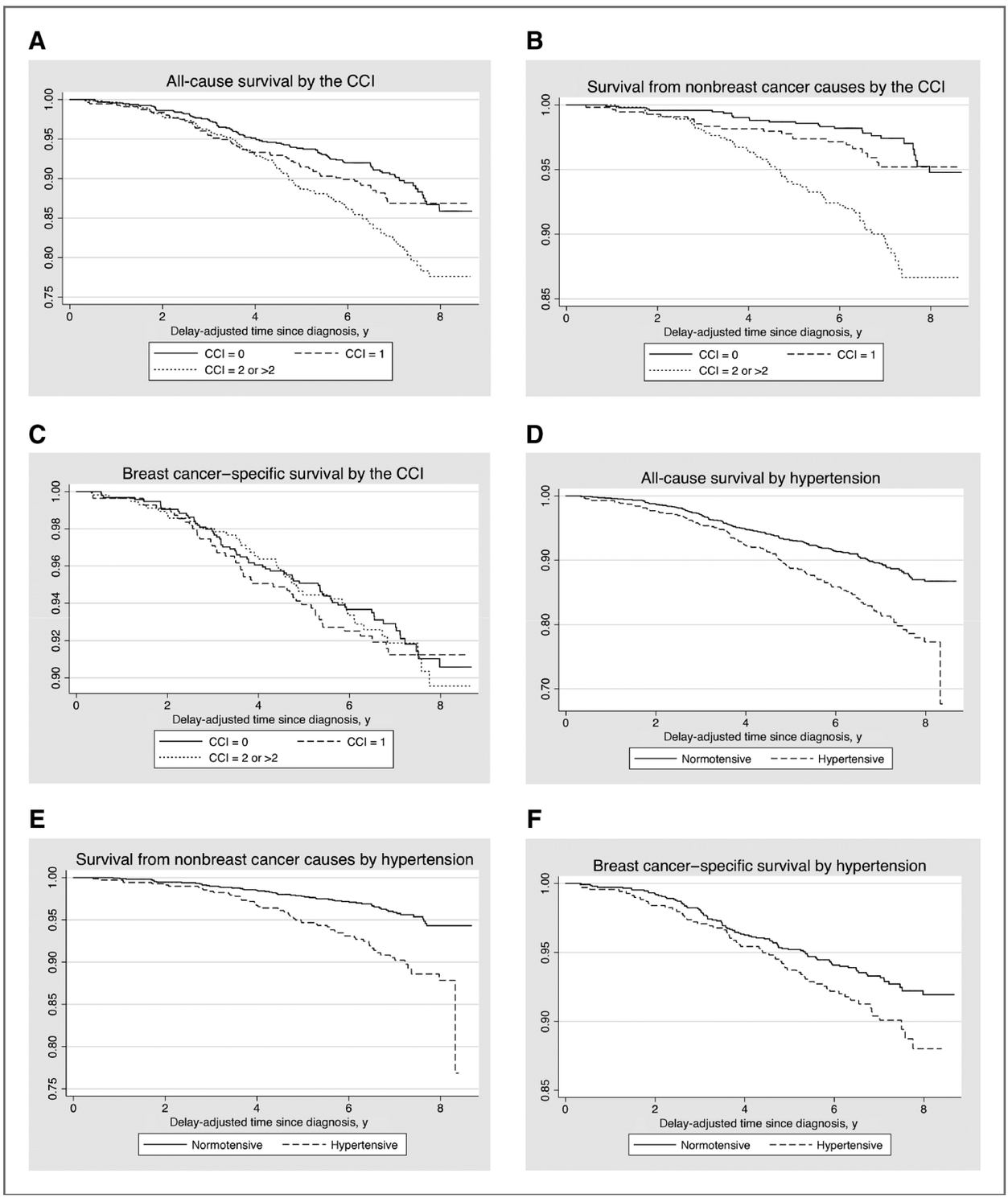


**Figure 2.** Kaplan–Meier survival curves. A, overall survival by the Charlson comorbidity index score. B, survival from nonbreast cancer causes by the Charlson comorbidity index score. C, breast cancer–specific survival by the Charlson comorbidity index score. D, overall survival by hypertension. E, survival from nonbreast cancer causes by hypertension. F, breast cancer–specific survival by hypertension.

**Table 2.** Univariate and multivariable HRs for CCI and hypertension

| | Overall risk of death[a] | | Risk of death from nonbreast cancer causes[a] | | Breast cancer–specific risk of death[a] | |
|---|---|---|---|---|---|---|
| | *n* (deaths) | HR (95% CI) | *n*, deaths | HR (95% CI) | *n* (deaths) | HR (95% CI) |
| CCI | | | | | | |
| Unadjusted | 2,272 (291) | 1.48 (1.30–1.69) | 2,129 (107) | 2.09 (1.65–2.64) | 2,129 (184) | 1.15 (.97–1.37) |
| Adjusted | 2,125 (290) | 1.32 (1.13–1.54) | 2,125 (107) | 1.55 (1.19–2.02) | 2,125 (183) | 1.14 (0.93–1.41) |
| Hypertension | | | | | | |
| Unadjusted | 2,229 (307) | 1.73 (1.40–2.14) | 2,229 (118) | 2.33 (1.62–3.34) | 2,229 (189) | 1.36 (1.01–1.82) |
| Adjusted | 1,868 (220) | 1.55 (1.20–1.99) | 1,752 (97) | 1.67 (1.10–2.54) | 1,752 (123) | 1.47 (1.03–2.09) |
| Additionally adjusted for antihypertensive medication | 1,840 (220) | 1.18 (.70–1.97) | 1,752 (97) | 1.43 (.61–3.33) | 1,752 (123) | 1.10 (.56–2.13) |

NOTE: Statistical tests are based on delayed entry Cox proportional hazards models.

[a]Adjusted models include age, education, race/ethnicity, chemotherapy, radiation, tamoxifen, BMI, smoking, physical activity, stage, hormone receptor status and nodal status.

0.80–1.49), and stage III disease (HR, 0.53; 95% CI, 0.23–1.25). In multivariable models, there were no statistically significant interactions between comorbidity and tumor stage.

In adjusted models, the effect of hypertension increased across tumor stage strata, but the estimates were generally not statistically significant (Table 5).

## Discussion

We found that patient-reported comorbid conditions, assessed by the CCI following initial breast cancer treatment, were associated with a statistically significantly increased risk of death from overall and nonbreast cancer causes, but not from breast cancer specifically, in this cohort of 2,272 long-term breast cancer survivors. Notably, there was a dose–response relationship between the CCI and overall survival as well as that from nonbreast cancer causes. In addition, we found that comorbidity exerted most adverse effects among women with stage I disease and younger age at diagnosis. In addition to the independent effects of the CCI, hypertension, a common condition not included in the CCI, was also associated with a statistically significantly increased risk of death from overall and from nonbreast cancer causes, as well as breast cancer–specific death, but these associations were no longer statistically significant after we adjusted for antihypertensive medication.

Our results are consistent with those of other prospective and retrospective cohort studies of breast cancer survivors (3–5, 10, 17, 27–31). We extend these results to show that the adverse effects of comorbidity, as reflected by higher CCI scores, exert long-term effects, particularly among women with early-stage disease. Less data are available with regard to the effect of individual comorbidities that are not included in the CCI. Consistent with our previous retrospective cohort study of African American and white women (17), in this prospective analysis, we confirm the association of hypertension with breast cancer–specific survival as well as overall survival and that from nonbreast cancer causes, yet the association became attenuated after adjustment for antihypertensive treatment. Our ability

**Table 3.** Univariate and multivariable cox regression HRs by CCI

| | Overall risk of death HR (95% CI)[a] | | | Risk of death from nonbreast cancer causes HR (95% CI)[a] | | | Breast cancer–specific risk of death HR (95% CI)[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | ≥2 | 0 | 1 | ≥2 | 0 | 1 | ≥2 |
| CCI | | | | | | | | | |
| Unadjusted | 1.00 | 1.13 (.85–1.50) | 2.20 (1.71–2.83) | 1.00 | 1.62 (.95–2.78) | 4.17 (2.63–6.62) | 1.00 | 0.83 (.57–1.20) | 1.38 (.99–1.94) |
| Adjusted[a] | 1.00 | 1.06 (.76–1.47) | 1.72 (1.27–2.32) | 1.00 | 1.20 (.66–2.19) | 2.31 (1.37–3.90) | 1.00 | 0.89 (.58–1.36) | 1.32 (.88–1.98) |

[a]Adjusted models include age, education, race/ethnicity, chemotherapy, radiation, tamoxifen, BMI, smoking, physical activity, stage, hormone receptor status, and nodal status.

**Table 4.** Univariate and multivariable HRs for CCI stratified by women's age at breast cancer diagnosis and tumor stage

| | Overall risk of death | | Risk of death from nonbreast cancer causes | | Breast cancer–specific risk of death | |
|---|---|---|---|---|---|---|
| **Variable** | **Unadjusted HR (95% CI)** | **Adjusted[a] HR (95% CI)** | **Unadjusted HR (95% CI)** | **Adjusted[a] HR (95% CI)** | **Unadjusted HR (95% CI)** | **Adjusted[a] HR (95% CI)** |
| CCI | | | | | | |
| Women's age at breast cancer diagnosis, y | | | | | | |
| <50 | 1.19 (.83–1.71) | 1.49 (.91–2.43) | 2.20 (0.87–5.55) | Not calculable[a] | 1.03 (0.68–1.55) | 1.17 (0.65–2.08) |
| 50–64 | 1.44 (1.16–1.77) | 1.42 (1.12–1.80) | 1.99 (1.28–3.09) | 1.84 (1.11–3.05) | 1.31 (1.01–1.70) | 1.30 (.98–1.74) |
| 65–79 | 1.29 (1.05–1.58) | 1.17 (0.94–1.47) | 1.51 (1.11–2.04) | 1.29 (0.94–1.78) | 0.96 (0.69–1.32) | 0.91 (0.64–1.30) |
| Women's tumor stage | | | | | | |
| I | 1.75 (1.38–2.22) | 1.65 (1.26–2.16) | 2.08 (1.43–3.02) | 1.82 (1.22–2.72) | 1.29 (0.90–1.85) | 1.31 (0.86–2.00) |
| IIa | 1.63 (1.31–2.02) | 1.33 (1.02–1.74) | 2.04 (1.41–2.96) | 1.29 (0.84–1.98) | 1.40 (1.03–1.89) | 1.42 (0.97–2.08) |
| IIb | 1.19 (0.91–1.54) | 1.09 (0.80–1.49) | 2.21 (1.29–3.80) | 1.83 (0.92–3.65) | 0.95 (0.69–1.30) | 0.96 (0.66–1.38) |
| III | 0.90 (.54–1.50) | 0.53 (.23–1.25) | Not calculable[b] | Not calculable[b] | 0.82 (.48–1.42) | 0.45 (.18–1.10) |

NOTE: The results represent HR for 1 unit increase in CCI and the CCI categories are 0, 1, and $\geq$2.

[a]Adjusted models include age, education, race/ethnicity, chemotherapy, radiation, tamoxifen, BMI, smoking, physical activity, stage, hormone receptor status, and nodal status.

[b]Insufficient number of deaths to compute HRs in this subgroup.

to adjust for tumor characteristics, other comorbidity, BMI, and lifestyle factors in the analysis was a strength. A previous cohort study conducted in the 1970s also showed an association of diagnosed hypertension with cancer mortality (32). Similarly, a more recent study by Jung and colleagues (33) found that hypertension was related to survival of patients with metastatic breast cancer when age and other covariates were controlled for in the analysis (33). Notably, an important limitation of the latter study (33) is that the effect of antihypertensive medication was not taken into account.

To show that hypertension is truly causally associated with breast cancer outcomes, it will be important to elucidate underlying biologic mechanisms. For example, increased expression of inositol triphosphate and cytosolic calcium have been hypothesized to be involved in the pathogenesis of hypertension and in the early events of cell proliferation that are activated by endogenous oncogenes (34). Another study has identified aberrant carcinogen binding to DNA in lymphocytes of hypertensive patients (35). Cell death via apoptosis can also affect the growth of vascular smooth muscle cells, and related aberrations have also been found in hypertension (36). Furthermore, neurohormones such as angiotensin II, catecholamines, vasopressin, insulin, and growth hormone regulate blood pressure and have a mitogenic effect (37). Further research is needed to determine specific mechanisms by which hypertension may aggravate breast cancer and lead to adverse patient outcomes, and how antihypertensive medications may counteract these effects. This study shows that hypertensive patients were less likely to receive chemotherapy or radiotherapy, which may further contribute to poorer prognosis in this patient population.

Cancer stage and other tumor markers may modify the impact of comorbidity on survival among cancer patients, including those with breast cancer. Read and colleagues (38) showed that the effect of comorbidity was greatest among patients with localized disease at diagnosis and least in patients with advanced disease. Consistent with our results, survival was found to be more variable among women with localized disease, compared with those with regional and remote disease. Our finding that women with comorbidity, as reflected by higher CCI scores, were less likely to receive chemotherapy and radiotherapy is consistent with our previous report showing that breast cancer patients with functional limitations were also less likely to receive adjuvant therapy (39). Furthermore, West and colleagues (4) showed that patients with substantial comorbidity, as assessed with the CCI (15, 16), received less adjuvant breast cancer treatment including radiotherapy and chemotherapy. Moreover, several studies have indicated that comorbidity significantly affected treatment independent of age (40, 41). For example, Frasci and colleagues (42) showed that severe comorbidity based on the CCI was related to early termination of treatment for older patients with advanced non–small cell lung cancer enrolled in a clinical chemotherapy trial.

This study had design strengths and limitations. It included a large cohort of breast cancer patients from a large, integrated health care delivery system in Northern California (whose members are representative of the

**Table 5.** Univariate and multivariable HRs for hypertension stratified by women's age at breast cancer diagnosis and tumor stage

| | Overall risk of death | | | Risk of death from nonbreast cancer causes | | | Breast cancer–specific risk of death | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Unadjusted HR (95% CI) | Adjusted[a] HR (95% CI) | Further adjusted for HTN med[b] HR (95% CI) | Unadjusted HR (95% CI) | Adjusted[b] HR (95% CI) | Further adjusted for HTN med[b] HR (95% CI) | Unadjusted HR (95% CI) | Adjusted[b] HR (95% CI) | Further adjusted for HTN med[b] HR (95% CI) |
| HTN Women's age at breast cancer diagnosis, y | | | | | | | | | |
| <50 | 1.29 (0.51–3.29) | 0.59 (0.11–3.10) | 50 (0.049–5.13) | 1.79 (0.21–15.36) | 1.42 (0.16–12.67) | 1.99 (0.04–91.78) | 1.20 (0.42–3.42) | 1.20 (0.42–3.42) | 53 (0.07–4.18) |
| 50–64 | 1.73 (1.18–2.54) | 1.51 (1.00–2.27) | 1.68 (0.76–3.76) | 2.20 (1.11–4.36) | 1.84 (0.86–3.94) | 1.97 (0.48–8.13) | 1.55 (0.98–2.47) | 1.55 (0.98–2.47) | 1.40 (0.81–2. 43) |
| 65–79 | 1.25 (0.89–1.76) | 1.31 (0.90–1.90) | 1.05 (0.52–2.09) | 1.30 (0.83–2.02) | 1.35 (0.82–2.21) | 1.16 (0.43–3.13) | 1.19 (0.69–2.04) | 1.19 (0.69–2.04) | 1.44 (0.78–2.66) |
| Women's tumor stage | | | | | | | | | |
| I | 2.09 (1.37–3.19) | 2.24 (1.28–3.92) | 1.45 (0.52- 4.09) | 2.24 (1.28–3.92) | 1.16 (0.61–2.21) | 1.22 (0.25–5.91) | 1.91 (1.00–3.64) | 2.39 (1.13–5.05) | 2.25 (0.59–8.59) |
| IIa | 1.89 (1.27–2.82) | 3.00 (1.63–5.49) | 1.25 (.54–2.90) | 3.00 (1.63–5.49) | 1.89 (0.91–3.94) | 2.37 (0.73–7.74) | 1.29 (0.74–2.25) | 1.16 (0.58–2.31) | 0.71 (0.21–2.36) |
| IIb | 2.07 (1.31–3.26) | 1.98 (0.88–4.46) | 2.95 (1.07–8.12) | 1.98 (0.88–4.46) | 3.45 (1.03–11.5) | 0.87 (0.06–12.93) | 2.11 (1.22–3.65) | 2.48 (1.25–4.89) | 3.01 (1.07–8.46) |
| III | 0.24 (.57–1.05) | 0.14 (.03-.72) | 0.05 (0.00–0.65) | Not calculable[c] | Not calculable[c] | Not calculable[c] | 0.26 (.06–1.12) | 0.15 (.03–0.75) | 0.05 (0.00–0.68) |

[a]Adjusted models include age, education, race/ethnicity, CCI, chemotherapy, radiation, tamoxifen, BMI, smoking, physical activity, stage, hormone receptor status and nodal status.
[b]Adjusted for antihypertensive medication in addition to all of the aforementioned covariates; namely, age, education, race/ethnicity, CCI, chemotherapy, radiation, tamoxifen, BMI, smoking, physical activity, stage, hormone receptor status and nodal status.
[c]Insufficient number of deaths to compute HRs in this subgroup.

general population with respect to most demographic and socioeconomic categories; ref. 15) and the Utah Cancer Registry, with long follow-up and a broad age range at diagnosis. Comorbidity data were collected through patient questionnaires, which are deemed reliable and valid (14), as shown in previous studies of breast cancer patients (43, 44). Although more than 2,000 cases of breast cancer were included in the cohort, we had limited statistical power to examine individual causes of death. Further investigation of the impact of comorbidity on cause-specific death (e.g., cardiovascular disease, diabetes) may reveal mechanisms by which comorbid conditions exert their effects. Because this study is a prospective analysis of breast cancer survivors, comorbidity assessments were conducted after initial breast cancer treatment and thus we were unable to determine whether the mortality increase due to comorbidity is higher in women with breast cancer than in their counterparts without the disease.

In summary, in this prospective study of breast cancer survivors, a CCI score of $\geq$1 was present in 54% of women, and reported comorbidity following initial breast cancer treatment was associated with a reduction in overall survival and that from nonbreast cancer causes. The adverse impact of comorbidity on survival was stronger among women with stage I disease. Importantly, women with early-stage breast cancer form the majority of contemporary breast cancer survivors in the developed world today (45). Our observations, combined with those of other investigators, suggest that failure to manage comorbidity may have important consequences for longevity among breast cancer survivors. Specifically, if comorbidities are well controlled, breast cancer patients may be better positioned to complete their prescribed chemotherapy and other aggressive regimens. Consequently, the duration and quality of their survival may be enhanced.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** D. Braithwaite, W.A. Satariano, B.J. Caan
**Development of methodology:** D. Braithwaite, D.H. Moore, B.J. Caan
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** D. Braithwaite, B.J. Caan
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** D. Braithwaite, D.H. Moore, W.A. Satariano, M.L. Kwan, R.A. Hiatt, C. Kroenke, B.J. Caan
**Writing, review, and/or revision of the manuscript:** D. Braithwaite, D.H. Moore, W.A. Satariano, M.L. Kwan, R.A. Hiatt, C. Kroenke, B.J. Caan
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** D. Braithwaite, R.A. Hiatt
**Study supervision:** D. Braithwaite, R.A. Hiatt, B.J. Caan

## Grant Support

This research was supported by a career development award to D. Braithwaite from the NIH, National Cancer Institute, Bay Area Breast Cancer SPORE (P50 CA 58207), and the Hellman Fellowship at the University of California, San Francisco. The data are from the Life after Cancer Epidemiology (LACE) study, which is supported by the National

Cancer Institute (R01 CA129059). D. Braithwaite was also in part supported by the Mentored Research Scholar Award (121891-MRSG-12-007-01-CPHPS) from the American Cancer Society.

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

Received December 31, 2011; revised April 9, 2012; accepted April 30, 2012; published OnlineFirst May 9, 2012.

## References

1. American Cancer Society. Cancer facts and figures; 2011.
2. Bigby J, Holmes MD. Disparities across the breast cancer continuum. Cancer Causes Control 2005;16:35–44.
3. 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;294:1765–72.
4. West DW, Satariano WA, Ragland DR, Hiatt RA. Comorbidity and breast cancer survival: a comparison between black and white women. Ann Epidemiol 1996;6:413–9.
5. Hershman D, McBride R, Jacobson JS, Lamerato L, Roberts K, Grann VR, et al. Racial disparities in treatment and survival among women with early-stage breast cancer. J Clin Oncol 2005;23:6639–46.
6. Tammemagi CM. Racial/ethnic disparities in breast and gynecologic cancer treatment and outcomes. Curr Opin Obstet Gynecol 2007;19:31–6.
7. Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. Cancer 1997;80:1273–83.
8. Yancik R, Havlik RJ, Wesley MN, Ries L, Long S, Rossi WK, et al. Cancer and comorbidity in older patients: a descriptive profile. Ann Epidemiol 1996;6:399–412.
9. Yancik R. Epidemiology of cancer in the elderly. Current status and projections for the future. Rays 1997;22(1 Suppl):3–9.
10. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med 1994;120:104–10.
11. Stricker CT, Jacobs LA, Risendal B, Jones A, Panzer S, Ganz PA, et al. Survivorship care planning after the Institute of Medicine recommendations: how are we faring? J Cancer Surviv 2011;5:358–70.
12. Caan B, Sternfeld B, Gunderson E, Coates A, Quesenberry C, Slattery ML. Life After Cancer Epidemiology (LACE) Study: a cohort of early stage breast cancer survivors (United States). Cancer Causes Control 2005;16:545–56.
13. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 2007;298:289–98.
14. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? Med Care 1996;34:73–84.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
16. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–51.
17. Braithwaite D, Tammemagi CM, Moore DH, Ozanne EM, Hiatt RA, Belkora J, et al. Hypertension is an independent predictor of survival disparity between African-American and white breast cancer patients. Int J Cancer 2009;124:1213–9.
18. Emaus A, Veierod MB, Tretli S, Finstad SE, Selmer R, Furberg AS, et al. Metabolic profile, physical activity, and mortality in breast cancer patients. Breast Cancer Res Treat 2010;121:651–60.
19. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Arch Intern Med 1998;158:1855–67.
20. Staten LK, Taren DL, Howell WH, Tobar M, Poehlman ET, Hill A, et al. Validation of the Arizona activity frequency questionnaire using doubly labeled water. Med Sci Sports Exerc 2001;33:1959–67.
21. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32(9 Suppl):S498–504.
22. Fleming ID, Cooper JS, Henson DE. AJCC Cancer staging manual. 5th ed. New York, NY: Lippincott-Raven 1997.
23. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340–9.
24. Cox DR, Oakes D. Analysis of survival data. Monographs in statistics and applied probability 21. New York, NY: Chapman & Hill; 1994.
25. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. Statistics for Biology and Health. New York: Springer-Verlag; 2000.
26. Prentice RL, Kalbfleisch JD. Hazard rate models with covariates. Biometrics 1979;35:25–39.
27. Nagel G, Wedding U, Hoyer H, Rohrig B, Katenkamp D. The impact of comorbidity on the survival of postmenopausal women with breast cancer. J Cancer Res Clin Oncol 2004;130:664–70.
28. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 2008;300:2754–64.
29. Patterson RE, Flatt SW, Saquib N, Rock CL, Caan BJ, Parker BA, et al. Medical comorbidities predict mortality in women with a history of early stage breast cancer. Breast Cancer Res Treat 2010;122:859–65.
30. Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst 2011;103:1101–11.
31. Land LH, Dalton SO, Jensen MB, Ewertz M. Impact of comorbidity on mortality: a cohort study of 62,591 Danish women diagnosed with early breast cancer, 1990–2008. Breast Cancer Res Treat 2012;131:1013–20.
32. Dyer AR, Stamler J, Berkson DM, Lindberg HA, Stevens E. High blood-pressure: a risk factor for cancer mortality? Lancet 1975;1:1051–6.
33. Jung SY, Rosenzweig M, Linkov F, Brufsky A, Weissfeld JL, Sereika SM. Comorbidity as a mediator of survival disparity between younger and older women diagnosed with metastatic breast cancer. Hypertension 2012;59:205–11.
34. Meyer P. Increased intracellular calcium: from hypertension to cancer. J Hypertens Suppl 1987;5:S3–4.
35. Norden A, Schersten B, Thulin T, Pero RW, Bryngelsson C, Mitelman F. Letter: hypertension related to DNA repair synthesis and carcinogen uptake. Lancet 1975;2:1094.
36. Hamet P. Cancer and hypertension. An unresolved issue. Hypertension 1996;28:321–4.
37. Extermann M. Interaction between comorbidity and cancer. Cancer Control 2007;14:13–22.
38. Read WL, Tierney RM, Page NC, Costas I, Govindan R, Spitznagel EL, et al. Differential prognostic impact of comorbidity. J Clin Oncol 2004;22:3099–103.
39. Braithwaite D, Satariano WA, Sternfeld B, Hiatt RA, Ganz PA, Kerlikowske K, et al. Long-term prognostic role of functional limitations among women with breast cancer. J Natl Cancer Inst 2010;102:1468–77.
40. Greenfield S, Blanco DM, Elashoff RM, Ganz PA. Patterns of care related to age of breast cancer patients. JAMA 1987;257:2766–70.
41. Newschaffer CJ, Bush TL, Penberthy LT. Comorbidity measurement in elderly female breast cancer patients with administrative and medical records data. J Clin Epidemiol 1997;50:725–33.

**42.** Frasci G, Lorusso V, Panza N, Comella P, Nicolella G, Bianco A, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 2000;18:2529–36.

**43.** Satariano WA, Ragland DR. Upper-body strength and breast cancer: a comparison of the effects of age and disease. J Gerontol A Biol Sci Med Sci 1996;51:M215–9.

**44.** Satariano WA, Ragland DR, DeLorenze GN. Limitations in upper-body strength associated with breast cancer: a comparison of black and white women. J Clin Epidemiol 1996;49: 535–44.

**45.** Smigal C, Jemal A, Ward E, Cokkinides V, Smith R, Howe HL, et al. Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin 2006;56:168–83.