

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

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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 non-melanoma 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.

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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

CCI Weight	Comorbid conditions
0	No comorbid conditions
1	Heart attack (myocardial infarction) Peripheral arterial disease Other diagnosed heart problems Stroke Asthma Ulcer disease Insulin-dependent diabetes Arthritis
2	Renal disease/kidney stones 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).

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.

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 χ^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 ≥ 1 was present in 54% of patients. The proportion of women with a CCI score of ≥ 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 ≥ 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 ≥ 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 ≥ 2 were less physically active compared with women with a CCI score of 0 (MET h/wk: ≥ 46 mean = 435 vs. 218, respectively, $P = .006$). Furthermore, patients with a CCI score of ≥ 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 ≥ 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)	<0.001
50–64	1,037 (45.7)	472 (46.7)	280 (46.8)	231 (44.3)	
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)	=0.008
College	842 (37.2)	367 (36.3)	240 (40.1)	192 (36.9)	
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)	=0.001
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)	
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)	<0.001
25–30	650 (34.0)	288 (33.8)	175 (34.2)	149 (34.3)	
>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)	=0.054
Past	894 (39.4)	380 (37.6)	233 (38.9)	221 (42.3)	
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)	= 0.653
Past	159 (7.0)	71 (7.06)	42 (7.0)	38 (7.3)	
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)	=0.157
IIA	762 (33.6)	365 (36.2)	182 (30.4)	168 (32.3)	
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.

^aP values were computed using Pearson χ^2 tests for categorical variables.

^bBreast-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,

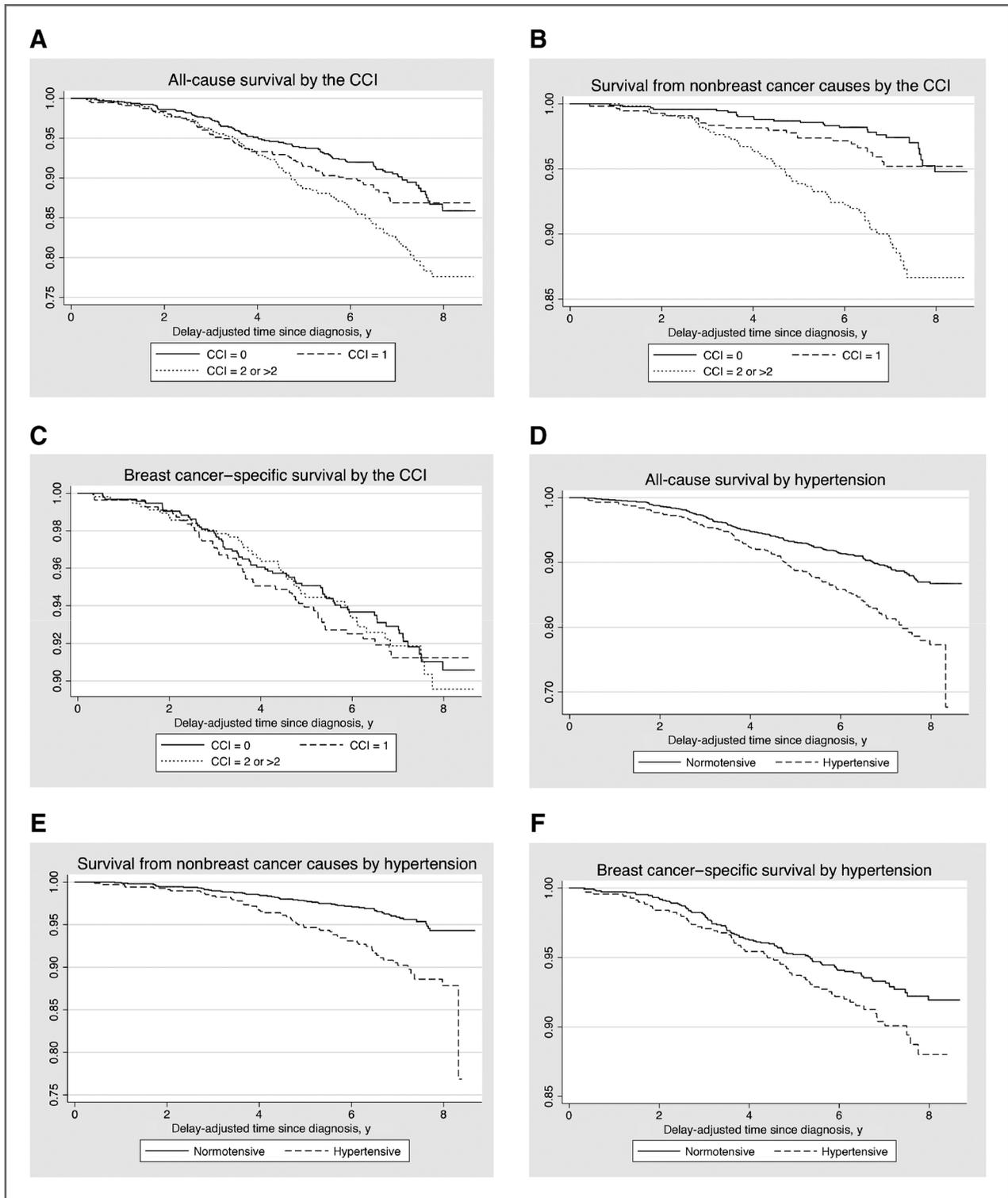


Figure 2. Kaplan-Meier survival curves. A, overall survival by the Charlson comorbidity index score. B, survival from nonbreast cancer causes by the Charlson comorbidity index score. C, breast cancer-specific survival by the Charlson comorbidity index score. D, overall survival by hypertension. E, survival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

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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.

^aAdjusted 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)

^aAdjusted 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

Variable	Overall risk of death		Risk of death from nonbreast cancer causes		Breast cancer-specific risk of death	
	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)
Ila	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)
Ilb	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 ≥ 2 .

^aAdjusted models include age, education, race/ethnicity, chemotherapy, radiation, tamoxifen, BMI, smoking, physical activity, stage, hormone receptor status, and nodal status.

^bInsufficient 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 fur-

ther 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

Variable	Overall risk of death			Risk of death from nonbreast cancer causes			Breast cancer-specific risk of death		
	Unadjusted	Adjusted ^a	Further adjusted for HTN med ^b	Unadjusted	Adjusted ^b	Further adjusted for HTN med ^b	Unadjusted	Adjusted ^b	Further adjusted for HTN med ^b
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	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)
Ila	1.89 (1.27–2.82)	3.00 (1.63–5.49)	1.25 (0.54–2.90)	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)
Ilb	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 (0.57–1.05)	0.14 (0.03–0.72)	0.05 (0.00–0.65)	Not calculable ^c	Not calculable ^c	Not calculable ^c	0.26 (0.06–1.12)	0.15 (0.03–0.75)	0.05 (0.00–0.68)

^aAdjusted models include age, education, race/ethnicity, CCI, chemotherapy, radiation, tamoxifen, BMI, smoking, physical activity, stage, hormone receptor status and nodal status.

^bAdjusted 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.

^cInsufficient 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 ≥ 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.

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