Published OnlineFirst November 25, 2014; DOI: 10.1158/1055-9965.EPI-14-1140

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Diabetes and Other Comorbidities in Breast Cancer Survival by Race/Ethnicity: The California Breast Cancer Survivorship Consortium (CBCSC)

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Abstract

Background: The role of comorbidities in survival of patients with breast cancer has not been well studied, particularly in nonwhite populations.

Methods: We investigated the association of specific comorbidities with mortality in a multiethnic cohort of 8,952 breast cancer cases within the California Breast Cancer Survivorship Consortium (CBCSC), which pooled questionnaire and cancer registry data from five California-based studies. In total, 2,187 deaths (1,122 from breast cancer) were observed through December 31, 2010. Using multivariable Cox proportional hazards regression, we estimated HRs and 95% confidence intervals (CI) for overall and breast cancer–specific mortality associated with previous cancer, diabetes, high blood pressure (HBP), and myocardial infarction.

Results: Risk of breast cancer–specific mortality increased among breast cancer cases with a history of diabetes (HR, 1.48; 95% CI, 1.18–1.87) or myocardial infarction (HR, 1.94; 95% CI, 1.27–2.97). Risk patterns were similar across race/ethnicity (non-Latina white, Latina, African American, and Asian American), body size, menopausal status, and stage at diagnosis. In subgroup analyses, risk of breast cancer–specific mortality was significantly elevated among cases with diabetes who received neither radiotherapy nor chemotherapy (HR, 2.11; 95% CI, 1.32–3.36); no increased risk was observed among those who received both treatments (HR, 1.13; 95% CI, 0.70–1.84; $P_{\text{interaction}} = 0.03$). A similar pattern was found for myocardial infarction by radiotherapy and chemotherapy ($P_{\text{interaction}} = 0.09$).

Conclusion: These results may inform future treatment guidelines for patients with breast cancer with a history of diabetes or myocardial infarction.

Impact: Given the growing number of breast cancer survivors worldwide, we need to better understand how comorbidities may adversely affect treatment decisions and ultimately outcome. *Cancer Epidemiol Biomarkers Prev; 24(2); 361–8. ©2014 AACR.*

Introduction

The presence of chronic illnesses or comorbidities at the time of breast cancer diagnosis is common. In an analysis based on Medicare claims data, 42% of patients with breast cancer had one or more comorbidities near the time of diagnosis (1), and patients with breast cancer with one or more comorbid conditions have been shown to experience significantly worse survival (2). The current evidence, however, has some limitations, including the use of summary indices such as the Charlson Comorbidity Index, which does not consider the influence of individual comorbidities on prognosis, the focus on overall mortality only, and the lack of information on lifestyle-related factors that could modify the observed associations.

Specific comorbidities may account for some of the racial/ethnic survival differences after breast cancer diagnosis; however, most prior studies have been limited by relatively small sample sizes and lack of information on some racial/ethnic groups (Asian Americans, Latinas). The prevalence of hypertension (3, 4) and diabetes (3) is higher in African American than white patients with breast cancer and associations have been reported between these comorbidities and overall mortality (3) and between hypertension and breast cancer–specific mortality (4).

To better understand the association of specific comorbidities with overall mortality and breast cancer–specific mortality by race/ethnicity, we analyzed data from the California Breast Cancer Survivorship Consortium (CBCSC; ref. 5). We considered duration and treatment of comorbidities, as well as stage at diagnosis and treatment for breast cancer, to explore reasons for the potential adverse effects of comorbidities on survival.

Materials and Methods

The California Breast Cancer Survivorship Consortium

This analysis included five studies from the CBCSC, which was established in 2011 to better understand racial/ethnic disparities in survival (5). They include three population-based case–control

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doi: 10.1158/1055-9965.EPI-14-1140

Published OnlineFirst November 25, 2014; DOI: 10.1158/1055-9965.EPI-14-1140

studies of breast cancer [the Asian American Breast Cancer Study (AABCS; ref. 6); the Women's Contraceptive and Reproductive Experiences study (CARE; ref. 7); and the San Francisco Bay Area Breast Cancer Study (SFBCS; ref. 8)], one breast cancer survivor cohort [the Life after Cancer Epidemiology (LACE) Study; ref. 9], and one cohort study [the California Teachers Study (CTS; ref. 10)]. The CTS cohort identified newly diagnosed breast cancer cases through annual linkages with the California Cancer Registry (CCR). The CBCSC harmonized and pooled questionnaire data from the individual studies and assembled uniform CCR data on clinical characteristics and mortality. The study was approved by the Institutional Review Boards of all participating institutions and the California State Committee for the Protection of Human Subjects.

Comorbidity variables, covariates, and clinicopathologic factors

We obtained patient information on comorbid conditions [diabetes, high blood pressure (HBP) or hypertension, myocardial infarction, or heart attack] from questionnaires. Questions on comorbidities were similar in the three case–control studies, which conducted in-person interviews on average 3 to 18 months after breast cancer diagnosis that queried for physician diagnoses that occurred before diagnosis, the age when first diagnosed, and treatment for the condition. In AABCS and CARE, questions on diabetes, HBP, and myocardial infarction were asked. In SFBCS, questions on diabetes and HBP were added later and the information is available on 41% of patients. In the CTS, participants completed self-administered questionnaires before breast cancer diagnosis that asked about diabetes, myocardial infarction, and HBP at the time of study enrollment. Conditions that were diagnosed after the completion of the baseline questionnaires were not captured. CTS participants were asked to check "yes" if they had the condition but were not asked when they were diagnosed with the condition. In LACE, participants were asked whether they were ever told by a doctor or other health professional of having diabetes, HBP, or myocardial infarction and when they were first told. Only conditions that occurred before the date of breast cancer diagnosis were considered.

CBCSC participants were linked to the CCR (5) to obtain information on previous cancer (excluding nonmelanoma skin cancer), American Joint Committee on Cancer (AJCC) stage, estrogen receptor (ER), and progesterone receptor (PR) status, nodal positivity, grade, tumor size, surgery type, chemotherapy, hormonal therapy, radiotherapy, marital status, and block-group composite measure of socioeconomic status (SES) of residence at diagnosis (11).

Statistical analysis

Cox proportional hazards regression models with attained age as the time scale and study as a stratification variable were used to estimate adjusted HRs and 95% confidence intervals (CI) in overall and race/ethnicity-specific models (5). The entry date was the date of diagnosis for women in the CTS or the date of interview for the case–control studies and LACE. The exit date was the date of death or end of follow-up (December 31, 2010), whichever occurred first. Analytic endpoints included overall and breast cancer–specific mortality. Deaths from breast cancer were identified from underlying causes of death on the death certificate based on *International Classification of Diseases, Ninth Revision*, codes 174–175 or *International Classification of Diseases, Tenth Revision*, code C50.

Multivariable analyses adjusted for age at diagnosis, race/ethnicity, education, neighborhood SES, nativity (United States or foreign born), age at first birth, smoking status, alcohol consumption, body mass index (BMI), marital status, AJCC stage, grade, tumor size, nodal involvement, surgery type, ER/PR status, chemotherapy, and radiotherapy. Of the 10,212 patients with breast cancer available for this analysis, information on comorbidities other than previous cancer was available for patient subsets (8,946 for diabetes, 8,952 for HBP, and 8,108 for myocardial infarction). We conducted analyses mutually adjusted for previous cancer, diabetes, HBP, and myocardial infarction based on 8,108 patients when we considered all four conditions simultaneously. We considered severity of comorbidity based on self-reported duration of comorbidity and whether treatment was received for the comorbidity. We evaluated effect modification in the associations between comorbidity (diabetes, HBP, myocardial infarction) and mortality outcomes by menopausal status, BMI, and AJCC stage and by first course of breast cancer treatment (type of breast surgery, radiotherapy, and chemotherapy treatment) as recorded in the CCR. We also examined the effect of comorbidities in patients with and without previous cancer. Statistical significance of multiplicative interaction terms was estimated with the Wald test by including a cross-product term of the exposure and the potential effect modifier in the Cox models.

Results

Table 1 shows the prevalence and characteristics of patients with breast cancer with each type of comorbidity. The prevalence of HBP was high (27.7%), followed by previous cancer (6.8%), diabetes (5.5%), and myocardial infarction (1.7%). There were significant differences in the prevalence of all four conditions by age and race/ethnicity. Patients with these comorbidities were less likely to have received chemotherapy or radiotherapy.

History of previous cancer, diabetes, HBP, and myocardial infarction was associated with a significantly increased risk of overall mortality after adjustment for tumor characteristics and lifestyle factors (Table 2); results were similar after further adjustment for other comorbidities. The increased risk of breast cancer–specific mortality among patients with diabetes (HR, 1.48; 95% CI, 1.18–1.87) and myocardial infarction (HR, 1.94, 95% CI, 1.27–2.97) remained when we mutually adjusted for the other comorbidity and covariates, but the increased risk in relation to previous cancer was not statistically significant. HPB was not associated with breast cancer–specific mortality (Table 2).

Evaluating the comorbidity–mortality associations within the four major racial/ethnic groups (Table 2) shows that previous cancer was associated with overall mortality in Latinas and Asian Americans, but with breast cancer–specific mortality only among Latinas (HR, 3.20; 95% CI, 1.37–7.46). Diabetes was associated with increased overall mortality (HRs ranged from 1.54 to 3.04; all Ps < 0.05) and suggestive for breast cancer–specific mortality across all four groups, with the latter only statistically significant in non–Latina whites (HR, 1.63; 95% CI, 1.10–2.43). HBP was associated with overall mortality in non–Latina whites but not with breast cancer–specific mortality. In Asian Americans, HBP was associated with lower risk of breast cancer–specific mortality; this finding differed significantly from that in non–Latina whites ($P_{\text{interaction}} = 0.01$). History of myocardial infarction was associated with overall (HR, 1.44; 95% CI, 1.06–1.95) and breast

Published OnlineFirst November 25, 2014; DOI: 10.1158/1055-9965.EPI-14-1140

Table 1. Characteristics of patients with breast cancer with a history of comorbidities[a], CBCSC, diagnoses 1993–2007

	Previous cancer		Diabetes		HBP or hypertension		Myocardial infarction	
	Total	**Yes (%)**	**Total**	**Yes (%)**	**Total**	**Yes (%)**	**Total**	**Yes (%)**
	8,952	**605 (6.8)**	**8,946**	**489 (5.5)**	**8,952**	**2,479 (27.7)**	**8,108**	**136 (1.7)**
Age, y								
<40	511 (5.7)	13 (2.1)	511 (5.7)	15 (3.1)	511 (5.7)	32 (1.3)	456 (5.6)	0 (0)
40–49	1,752 (19.6)	72 (11.9)	1,751 (19.6)	72 (14.7)	1,752 (19.6)	273 (11.0)	1,491 (18.4)	13 (9.6)
50–59	2,662 (29.7)	147 (24.3)	2,659 (29.7)	125 (25.6)	2,662 (29.7)	682 (27.5)	2,435 (30.0)	23 (16.9)
60–69	2,229 (24.9)	163 (26.9)	2,229 (24.9)	163 (33.3)	2,229 (24.9)	751 (30.3)	2,054 (25.3)	34 (25.0)
≥70	1,798 (20.1)	210 (34.7)	1,796 (20.1)	114 (23.3)	1,798 (20.1)	741 (29.9)	1,672 (20.6)	66 (48.5)
P		<0.0001		<0.0001		<0.0001		<0.0001
Race/ethnicity								
Non–Latina white	5,683 (63.5)	455 (75.2)	5,682 (63.5)	171 (35.0)	5,683 (63.5)	1,391 (56.1)	5,550 (68.5)	96 (70.6)
African American	882 (9.9)	51 (8.4)	880 (9.8)	101 (20.7)	882 (9.9)	399 (16.1)	776 (9.6)	21 (15.4)
Latina	928 (10.4)	46 (7.6)	925 (10.3)	104 (21.3)	928 (10.4)	270 (10.9)	324 (4.0)	5 (3.7)
Asian American	1,354 (15.1)	48 (7.9)	1,354 (15.1)	109 (22.3)	1,354 (15.1)	392 (15.8)	1,354 (16.7)	12 (8.8)
Other	105 (1.2)	5 (0.8)	105 (1.2)	4 (0.8)	105 (1.2)	27 (1.1)	104 (1.3)	2 (1.5)
P		<0.0001		<0.0001		<0.0001		0.02
Neighborhood SES[b]								
Lowest	543 (6.1)	34 (5.6)	542 (6.1)	63 (12.9)	543 (6.1)	206 (8.3)	507 (6.3)	10 (7.4)
Lower-middle	1,105 (12.3)	70 (11.6)	1,103 (12.3)	104 (21.3)	1,105 (12.3)	372 (15.0)	969 (12.0)	17 (12.5)
Middle	1,669 (18.6)	133 (22.0)	1,668 (18.6)	116 (23.7)	1,669 (18.6)	492 (19.8)	1,492 (18.4)	35 (25.7)
Higher-middle	2,314 (25.8)	142 (23.5)	2,313 (25.9)	99 (20.2)	2,314 (25.8)	615 (24.8)	2,096 (25.9)	34 (25.0)
Highest	3,049 (34.1)	204 (33.7)	3,048 (34.1)	99 (20.2)	3,049 (34.1)	724 (29.2)	2,783 (34.3)	37 (27.2)
Unknown	272 (3.0)	22 (3.6)	272 (3.0)	8 (1.6)	272 (3.0)	70 (2.8)	261 (3.2)	3 (2.2)
P		0.25		<0.0001		<0.0001		0.27
Tumor stage (AJCC)								
I	4,381 (48.9)	328 (54.2)	4,378 (48.9)	202 (41.3)	4,381 (48.9)	1,214 (49.0)	4,013 (49.5)	79 (58.1)
II	3,674 (41.0)	217 (35.9)	3,671 (41.0)	225 (46.0)	3,674 (41.0)	1,029 (41.5)	3,290 (40.6)	45 (33.1)
III	503 (5.6)	27 (4.5)	503 (5.6)	31 (6.3)	503 (5.6)	127 (5.1)	443 (5.5)	6 (4.4)
IV	129 (1.4)	8 (1.3)	129 (1.4)	12 (2.5)	129 (1.4)	29 (1.2)	117 (1.4)	1 (0.7)
Unknown	265 (3.0)	25 (4.1)	265 (3.0)	19 (3.9)	265 (3.0)	80 (3.2)	245 (3.0)	5 (3.7)
P		0.014		0.024		0.32		0.56
Breast surgery								
None	141 (1.6)	19 (3.1)	141 (1.6)	13 (2.7)	141 (1.6)	41 (1.7)	126 (1.6)	2 (1.5)
Mastectomy	3,817 (42.6)	241 (39.8)	3,815 (42.6)	230 (47)	3,817 (42.6)	1,108 (44.7)	3,457 (42.6)	71 (52.2)
Breast-conserving surgery	4,982 (55.7)	345 (57.0)	4,978 (55.6)	246 (50.3)	4,982 (55.7)	1,326 (53.5)	4,513 (55.7)	63 (46.3)
Other	12 (0.1)	0 (0)	12 (0.1)	0 (0)	12 (0.1)	4 (0.2)	12 (0.1)	0 (0)
P		0.006		0.002		0.14		0.12
Chemotherapy								
No	4,898 (54.7)	392 (64.8)	4,894 (54.7)	284 (58.1)	4,898 (54.7)	1,545 (62.3)	4,507 (55.6)	102 (75.0)
Yes	3,910 (43.7)	203 (33.6)	3,908 (43.7)	197 (40.3)	3,910 (43.7)	905 (36.5)	3,470 (42.8)	33 (24.3)
Unknown	144 (1.6)	10 (1.7)	144 (1.6)	8 (1.6)	144 (1.6)	29 (1.2)	131 (1.6)	1 (0.7)
P		<0.0001		0.38		<0.0001		<0.0001
Radiotherapy								
No	4,187 (46.8)	307 (50.7)	4,185 (46.8)	255 (52.1)	4,187 (46.8)	1,220 (49.2)	3,848 (47.5)	77 (56.6)
Yes	4,765 (53.2)	298 (49.3)	4,761 (53.2)	234 (47.9)	4,765 (53.2)	1,259 (50.8)	4,260 (52.5)	59 (43.4)
P		0.04		0.02		0.013		0.08
BMI (kg/m^2)								
<25.0	4,657 (52.0)	336 (55.5)	4,534 (50.7)	120 (24.5)	4,534 (50.6)	844 (34.0)	4,278 (52.8)	57 (41.9)
25.0 to ≤29.9	2,469 (27.6)	150 (24.8)	2,589 (28.9)	133 (27.2)	2,592 (29.0)	832 (33.6)	2,301 (28.4)	41 (30.1)
30.0 to ≤34.9	1,032 (11.5)	67 (11.1)	1,032 (11.5)	135 (27.6)	1,032 (11.5)	473 (19.1)	842 (10.4)	22 (16.2)
≥35.0	562 (6.3)	32 (5.3)	559 (6.2)	88 (18.0)	562 (6.3)	268 (10.8)	465 (5.7)	12 (8.8)
Unknown	232 (2.6)	20 (3.3)	232 (2.6)	13 (2.7)	232 (2.6)	62 (2.5)	222 (2.7)	4 (2.9)
P		0.22		<0.0001		<0.0001		<0.0001

[a]No and unknown conditions are not shown for the five comorbidities.

[b]Neighborhood SES is measured using the Yost SES index, which is a composite measure of 7 Census indicator variables.

cancer–specific (HR, 1.82; 95% CI, 1.04–3.16) mortality in non–Latina whites; nonsignificant positive associations were found in African Americans and Asian Americans (Table 2).

Duration of and treatment for diabetes appeared to influence mortality (Table 3). Risk of breast cancer–specific mortality increased with increasing duration of diabetes. Patients with a history of diabetes preceding breast cancer diagnosis by ≥15 years showed highest breast cancer–specific mortality (HR, 1.81; 95% CI, 1.17–2.81), the risk was intermediate among patients who had diabetes for 6 to 14 years (HR, 1.45; 95% CI, 0.92–2.27), and lowest among those who had diabetes for ≤5 years before breast cancer diagnosis (HR, 1.13; 95% CI, 0.76–1.69) compared with those without diabetes. Patients with breast cancer who reported treatment for diabetes did not show increased risk of breast cancer–specific mortality, whereas a significant 2-fold increased risk was observed among those who reported no treatment for diabetes (HR, 2.12; 95% CI, 1.25–3.63) or were unknown for treatment (HR, 2.02; 95% CI, 1.39–2.93). Similarly, there was a pattern of increasing risk of overall and breast cancer–specific mortality with longer duration since myocardial infarction.

Published OnlineFirst November 25, 2014; DOI: 10.1158/1055-9965.EPI-14-1140

Table 2. Race/ethnicity-specific associations between history of comorbidities and overall mortality and breast cancer–specific mortality, CBCSC, diagnoses 1993–2007

	Previous cancer		Diabetes		HBP or hypertension		Myocardial infarction	
	Overall HR (95% CI)	BC-specific HR (95% CI)	Overall HR (95% CI)	BC-specific HR (95% CI)	Overall HR (95% CI)	BC-specific HR (95% CI)	Overall HR (95% CI)	BC-specific HR (95% CI)
All patients[a]	1.30 (1.12–1.50)	1.11 (0.87–1.40)	1.75 (1.50–2.05)	1.48 (1.18–1.87)	1.15 (1.05–1.27)	0.91 (0.79–1.06)	1.45 (1.15–1.92)	1.94 (1.27–2.97)
Non–Latina whites[b]	1.18 (0.99–1.41)	1.09 (0.81–1.47)	1.94 (1.52–2.47)	1.63 (1.10–2.43)	1.26 (1.12–1.42)	0.93 (0.76–1.14)	1.44 (1.06–1.95)	1.82 (1.04–3.16)
African Americans[b]	1.36 (0.85–2.17)	0.91 (0.48–1.71)	1.54 (1.06–2.22)	1.17 (0.72–1.90)	1.15 (0.88–1.51)	1.07 (0.78–1.47)	1.97 (0.99–3.93)	1.71 (0.70–4.13)
Latinas[b]	2.56 (1.36–4.77)	3.20 (1.37–7.46)	3.04 (1.92–4.81)	1.50 (0.71–3.17)	1.02 (0.70–1.48)	0.73 (0.41–1.28)	0.30 (0.01–28.6)	Not available
Asian Americans[b]	2.16 (1.23–3.86)	1.85 (0.77–4.46)	1.92 (1.31–2.84)	1.43 (0.84–2.44)	0.88 (0.64–1.20)[c]	0.52 (0.33–0.81)[d]	2.01 (0.69–5.82)	1.10 (0.15–8.33)

Abbreviation: BC, breast cancer.

[a]Adjusted for race/ethnicity, age, stage (AJCC), hormone receptor status, nodal involvement, grade, tumor size, surgery type, chemotherapy, radiotherapy, prior cancer, BMI, education, neighborhood SES, nativity, marital status, menopausal status, age at first birth, smoking, and alcohol consumption.

[b]As above, but no adjustment for race/ethnicity.

[c]$P_{interaction}$ of non–Latina white versus Asian American with hypertension for overall mortality = 0.03.

[d]$P_{interaction}$ of non–Latina white versus Asian American with hypertension for breast cancer–specific mortality = 0.01.

We also examined the combined effects of previous cancer and other comorbidities on mortality (Table 3). Women with a history of diabetes but no previous cancer showed significant increased risks of overall (HR, 1.77) and breast cancer–specific (HR, 1.46) mortality; those who had both diabetes and previous cancer had even higher overall (HR, 3.02) and breast cancer–specific (HR, 2.10) mortality. Similarly, patients with a history of myocardial infarction, but no previous cancer had significantly elevated overall (HR, 1.48) and breast cancer–specific (HR, 1.86) mortality. Overall mortality was more than 3-fold higher among those with both previous cancer and myocardial infarction (HR, 3.33), but for breast cancer–specific mortality, the increased risk was not statistically significant. Overall mortality was significantly increased for those with HBP but no previous cancer (HR, 1.18) as well as for those with HBP and previous cancer (HR, 1.67), but there were no significant associations with breast cancer–specific mortality.

History of HBP was not associated with breast cancer–specific mortality irrespective of stage of breast cancer diagnosis (data not shown). In contrast, patients with early (stage I or II) or more advanced (stage III or IV) breast cancer and a history of diabetes showed elevated risk of breast cancer–specific mortality; the respective HRs were 1.49 (95% CI, 1.14–1.95) and 1.99 (1.24–3.19; data not shown). Patients with early-stage (I or II) breast cancer and history of myocardial infarction had a significant increased risk of breast cancer–specific mortality (HR, 1.90; 95% CI, 1.19–3.04); the increased risk among those with stage III/IV and myocardial infarction was not statistically significant (HR, 1.79; 95% CI, 0.64–4.96). The mortality patterns associated with diabetes, HBP, and myocardial infarction were similar by menopausal status and by BMI category (data not shown).

We investigated whether the association between comorbidities and mortality differed by breast cancer treatment (surgery, radiotherapy, chemotherapy). The mortality patterns associated with myocardial infarction or previous cancer did not differ between those who had a mastectomy or breast-conserving surgery (Table 4). Among patients with diabetes, the risk of overall mortality was significantly elevated irrespective of surgery type, whereas breast cancer–specific mortality was increased among those who had a mastectomy (HR, 1.60; 95% CI, 1.17–2.18), but not among those who had breast conserving surgery (HR, 1.07; 95% CI, 0.71–1.61; $P_{interaction} = 0.10$). In contrast, an increased

Table 3. Overall mortality and breast cancer–specific mortality in relation to diabetes, hypertension, and myocardial infarction by timing and treatment for comorbidity, and by history of previous cancer, CBCSC, diagnoses 1993–2007

	Diabetes		HBP or hypertension		Myocardial infarction	
	Overall HR[a] (95% CI)	Breast cancer–specific HR[a] (95% CI)	Overall HR[a] (95% CI)	Breast cancer–specific HR[a] (95% CI)	Overall HR[a] (95% CI)	Breast cancer–specific HR[a] (95% CI)
Duration of comorbidity before breast cancer diagnosis						
No comorbidity	1.00	1.00	1.00	1.00	1.00	1.00
Yes comorbidity ≤5 y	1.54 (1.17–2.02)	1.13 (0.76–1.69)	1.06 (0.89–1.27)	0.91 (0.71–1.16)	1.34 (0.83–2.16)[b]	1.41 (0.62–3.23)[b]
Yes comorbidity 6–14 y	2.02 (1.51–2.71)	1.45 (0.92–2.27)	1.24 (1.03–1.49)	1.03 (0.79–1.33)	1.93 (1.17–3.17)	2.00 (0.87–4.58)
Yes comorbidity ≥15 y	1.88 (1.38–2.57)	1.81 (1.17–2.81)	1.18 (0.97–1.44)	0.93 (0.70–1.24)		
Treated for comorbidity						
No comorbidity	1.00	1.00	1.00	1.00		
Yes condition, not treated	1.83 (1.16–2.89)	2.12 (1.25–3.63)	0.89 (0.58–1.36)	0.80 (0.48–1.32)	Not available	Not available
Yes condition, treated	1.69 (1.38–2.07)	1.13 (0.82–1.55)	1.13 (0.94–1.35)	0.95 (0.75–1.19)		
Yes condition, treated not known	2.06 (1.62–2.61)	2.02 (1.39–2.93)	1.24 (1.11–1.39)	0.96 (0.80–1.16)		
PC and comorbidity						
No PC, no comorbidity	1.00	1.00	1.00	1.00	1.00	1.00
No PC, yes comorbidity	1.77 (1.50–2.08)	1.46 (1.15–1.85)	1.18 (1.07–1.30)	0.95 (0.82–1.10)	1.48 (1.12–1.94)	1.86 (1.20–2.88)
Yes PC, no comorbidity	1.22 (1.04–1.43)	1.08 (0.84–1.39)	1.20 (1.00–1.45)	1.15 (0.87–1.51)	1.24 (1.06–1.45)	1.05 (0.81–1.35)
Yes PC, yes comorbidity	3.02 (2.01–4.54)	2.10 (0.98–4.86)	1.67 (1.33–2.09)	0.98 (0.62–1.55)	3.33 (1.71–6.49)	2.59 (0.63–10.57)

Abbreviation: PC, previous cancer.

[a]Adjusted for race/ethnicity, age, stage (AJCC), hormone receptor status, nodal involvement, grade, tumor size, surgery type, chemotherapy, radiotherapy, prior cancer, BMI, education, neighborhood SES, nativity, marital status, menopausal status, age at first birth, smoking, and alcohol consumption.

[b]Duration defined as number of years between diagnosis of comorbidity and diagnosis of breast cancer. For myocardial infarction, the cut points were <10 years and ≥10 years.

Published OnlineFirst November 25, 2014; DOI: 10.1158/1055-9965.EPI-14-1140

Table 4. Comorbidities and overall mortality and breast cancer–specific mortality stratified by type of breast surgery[a], CBCSC, diagnoses 1993–2007

	Overall mortality				Breast cancer–specific mortality			
	Mastectomy		Breast-conserving surgery		Mastectomy		Breast-conserving surgery	
	Death/no event	HR[b] (95% CI)	Death/no event	HR[b] (95% CI)	Death/no event	HR[b] (95% CI)	Death/no event	HR[b] (95% CI)
Diabetes[c]								
No	954/2,543	1.00	888/3,783	1.00	558/2,939	1.00	401/4,270	1.00
Yes	120/110	2.01 (1.62–2.50)	90/156	1.78 (1.40–2.28)	56/174	1.60 (1.17–2.18)	31/215	1.07 (0.71–1.61)
$P_{interaction}$				0.07				0.10
HBP or hypertension[c]								
No	712/1,967	1.00	602/3,034	1.00	455/2,224	1.00	305/3,331	1.00
Yes	380/728	1.04 (0.90–1.20)	389/941	1.39 (1.20–1.60)	163/945	0.80 (0.66–0.98)	132/1,198	1.12 (0.89–1.41)
$P_{interaction}$				0.02				0.06
Myocardial infarction[c]								
No	954/2,393	1.00	862/3,567	1.00	544/2,803	1.00	380/4,049	1.00
Yes	38/33	1.44 (1.02–2.03)	27/36	1.45 (0.96–2.19)	15/56	1.53 (0.89–2.63)	8/55	1.72 (0.81–3.63)
$P_{interaction}$				0.80				0.77
Previous cancer								
No	1,000/2,576	1.00	891/3,746	1.00	581/2,995	1.00	401/4,236	1.00
Yes	100/141	1.34 (1.08–1.66)	106/239	1.28 (1.04–1.58)	41/200	1.12 (0.80–1.57)	36/309	1.28 (0.89–1.83)
$P_{interaction}$				0.81				0.95

[a]Excluded patients who had no surgery (n = 141) or other type of surgery ($n = 12$).
[b]Adjusted for race/ethnicity, age, stage (AJCC), hormone receptor status, nodal involvement, grade, tumor size, radiotherapy, chemotherapy, prior cancer (except in the analysis on previous cancer), BMI, education, neighborhood SES, nativity, marital status, menopausal status, age at first birth, smoking, and alcohol consumption.
[c]Analyses on diabetes, HBP or hypertension, and myocardial infarction were based on 8,797, 8,905, and 8,062 patients, respectively, because of some missing data.

risk of overall mortality associated with HBP was observed among those who had breast-conserving surgery, but not among those who had a mastectomy ($P_{interaction} = 0.02$); the results for breast cancer–specific mortality were comparable (Table 4).

Risk of breast cancer–specific mortality was highest among patients with a history of diabetes who had received neither radiotherapy nor chemotherapy (HR, 2.11; 95% CI, 1.32–3,36; $P_{interaction} = 0.03$), intermediate among those who received either treatment (HR, 1.49; 95% CI, 1.05–2.11; $P_{interaction} = 0.47$), and lowest among those who received both treatments (HR, 1.13; 95% CI, 0.70–1.84) when compared with patients with breast cancer who had no diabetes with corresponding treatments (Table 5). A similar pattern of results was observed for diabetes and overall mortality when treatment with radiotherapy and chemotherapy was considered. There were no increased risks of overall or breast cancer–specific mortality in association with history of myocardial infarction for those treated with both chemotherapy and radiotherapy. However, patients with myocardial infarction, who received either radiotherapy or chemotherapy, or neither treatment showed significantly elevated risks of breast cancer–specific mortality (HR, 2.45 and 2.40, respectively) and overall mortality (HR, 1.95 and 1.64, respectively; Table 5).

Discussion

In this large, multiethnic study of patients with breast cancer followed an average of 9.8 ± 3.5 years, patients with a history of diabetes or myocardial infarction had 1.5- and 1.9-fold greater risk, respectively, of breast cancer–specific mortality than patients without these comorbidities after adjustment for other comorbidities, tumor characteristics, and lifestyle factors. These results were similar across racial/ethnic groups, BMI categories, menopausal status, and stage of breast cancer at diagnosis. However, higher risk of breast cancer–specific mortality appeared to be confined to patients not treated with radiotherapy or chemotherapy. The association was strongest for patients who reported no treatment for diabetes. Our findings on previous cancer in combination with diabetes and myocardial infarction suggest synergistic effects of these conditions. These results emphasize that the survival of patients with breast cancer may be compromised because of undertreatment for a specific comorbidity or for their breast cancer.

Diabetes is characterized by high levels of growth factors and inflammatory markers (12) which have been associated with carcinogenesis and adverse impact on breast cancer outcomes (13). Both cancer registry-based (1, 3, 14–17) and nonregistry based (18, 19) studies reported higher risk of overall mortality in diabetic breast cancer patients. Few studies have investigated the effects of diabetes on breast cancer–specific mortality; increased mortality was reported in two studies (18, 20), but not in a third study which also adjusted for BMI and other lifestyle factors (19). Our results strengthen the evidence that diabetes is associated with breast cancer–specific mortality. We were able to adjust for lifestyle factors, BMI, clinical, and pathologic factors as well as other comorbidities, and observed similar findings across racial/ethnic groups.

Our results on breast cancer–specific mortality and diabetes were strongest for patients with a long (≥15 year) history of diabetes, who reported no treatment for diabetes, had a history of previous cancer, or had neither chemotherapy nor radiotherapy treatment. The longer presence of diabetes or untreated diabetes may be associated with hyperinsulinemia related to underlying insulin resistance which may stimulate tumor growth (12). Although we do not have information on reasons for the lack of treatment for diabetes, it is plausible that patients who were treated for their diabetes may have fewer or less severe sequelae of diabetes, whereas those with a long history or uncontrolled diabetes may be more compromised, resulting in higher risk of end-organ symptoms (i.e., neuropathy, kidney failure), reducing their options for full-dose, effective breast cancer treatment. Patients with previous cancer may have already received lifetime maximum doses of specific chemotherapy, which may further reduce treatment options for their breast cancer. Patients who

Published OnlineFirst November 25, 2014; DOI: 10.1158/1055-9965.EPI-14-1140

Table 5. Comorbidities and overall mortality and breast cancer–specific mortality stratified by radiotherapy and chemotherapy, CBCSC, diagnoses 1993–2007

	Overall mortality						Breast cancer–specific mortality					
	Radiotherapy and chemotherapy						Radiotherapy and chemotherapy					
	Yes to both		Yes to either		No to both		Yes to both		Yes to either		No to both	
	Death/no event	HR[a] (95% CI)	Death/no event	HR[a] (95% CI)	Death/no event	HR[a] (95% CI)	Death/no event	HR[a] (95% CI)	Death/no event	HR[a] (95% CI)	Death/no event	HR[a] (95% CI)
Diabetes[b]												
No	513/1,601	1.00	801/3,068	1.00	605/1,708	1.00	392/1,722	1.0	423/3,446	1.0	197/2,116	1.00
Yes	39/62	1.56 (1.07–2.26)	107/122	1.73 (1.38–2.17)	75/84	2.34 (1.77–3.08)	22/79	1.13 (0.70–1.84)	45/184	1.49 (1.05–2.11)	28/131	2.11 (1.32–3.36)
$P_{interaction}$				0.62		0.04				0.47		0.03
HBP or hypertension[b]												
No	402/1,325	1.00	571/2,427	1.00	398/1,292	1.00	316/1,411	1.00	337/2,661	1.00	147/1,543	1.00
Yes	156/349	1.03 (0.83–1.28)	350/804	1.22 (1.06–1.42)	294/526	1.29 (1.09–1.54)	99/406	0.91 (0.70–1.18)	136/1,018	0.92 (0.74–1.15)	81/739	1.06 (0.76–1.46)
$P_{interaction}$				0.18		0.08				0.93		0.40
Myocardial infarction[b]												
No	478/1,449	1.00	804/2,921	1.00	611/1,637	1.00	360/1,567	1.00	419/3,306	1.00	199/2,049	1.00
Yes	4/11	0.73 (0.26–2.05)	26/36	1.95 (1.29–2.94)	37/22	1.64 (1.14–2.36)	2/13	0.53 (0.12–2.27)	11/51	2.45 (1.31–4.59)	11/48	2.40 (1.20–4.79)
$P_{interaction}$				0.05		0.11				0.07		0.09
Previous cancer												
No	530/1,614	1.00	836/3,050	1.00	608/1,709	1.00	395/1,749	1.0	434/3,452	1.00	214/2,103	1.00
Yes	34/74	1.18 (0.81–1.72)	92/193	1.26 (1.00–1.57)	88/124	1.48 (1.16–1.88)	23/85	1.10 (0.70–1.74)	41/244	1.31 (0.93–1.85)	15/197	0.84 (0.48–1.46)
$P_{interaction}$				0.26		0.14				0.34		0.50

[a]Adjusted for race/ethnicity, age, stage (AJCC), hormone receptor status, nodal involvement, grade, tumor size, surgery type, prior cancer (except in the analysis or previous cancer), BMI, education, neighborhood SES, nativity, marital status, menopausal status, age at first birth, smoking, and alcohol consumption.

[b]Analyses on diabetes, HBP or hypertension, and myocardial infarction were based on 8,785, 8,894, and 8,036 patients, respectively, because of some missing data.

were treated with chemotherapy or radiotherapy may be healthier than their counterparts who were not offered comparable therapy. Radiotherapy, chemotherapy, and other treatments are also less likely to be offered to patients with breast cancer with comorbidities, and treatment intensity and patient compliance may be lower (21–25). Thus our findings are consistent with studies which showed worse survival in the absence of radiotherapy and chemotherapy (16, 24, 26–28).

CBCSC patients with breast cancer with a history of myocardial infarction experienced increased overall and breast cancer–specific mortality irrespective of a prior cancer, but risks were higher among those who did not receive radiotherapy or chemotherapy. Patients with breast cancer with a history of cardiovascular disease experienced elevated overall mortality in two cancer registry-based studies (1, 16) and elevated breast cancer–specific mortality in another study (20), but not in two smaller, noncancer registry-based studies (18, 19). As noted above, the omission of radiotherapy may have adverse effects on recurrence rates and overall mortality (28–30). The lower receipt of chemotherapy among women with myocardial infarction may be related to concern that specific chemotherapy such as anthracyclines may have long-term cardiac toxicity in patients with breast cancer, particularly in older patients (31–33).

Our finding of an association of HBP with overall but not breast cancer–specific mortality is similar to the finding in the WHEL study (18). The reasons for the weaker associations with HBP in our study compared with two previous studies (3, 4) may be explained, in part, by smoking, alcohol consumption, and other factors that were not considered in previous studies. CBCSC Asian American women with HBP showed lower overall and breast cancer–specific mortality. These results are similar to those reported in Shanghai Chinese (19) and a study of mostly whites (17). Interestingly, the HBP–overall mortality association was stronger among women who had breast-conserving surgery (Table 4) and among patients who had either or neither radiotherapy and chemotherapy treatment (Table 5). Treatment for breast cancer as well as medications used to treat HBP (i.e., beta-blockers) may influence breast cancer survival (34); thus it will be important to include treatment information in future investigations.

Strengths of this study include the largest sample size to date to examine the impact of several common comorbidities on the risk of overall and breast cancer–specific mortality among racially and ethnically diverse breast cancer patients. We were able to adjust for most known prognostic and treatment-related factors as well as important lifestyle factors. In addition, we had information on age at diagnosis of the comorbidity and receipt of treatment for the specific comorbidity. Sensitivity analyses restricted to the three case–control studies that asked very similar questions on comorbidities confirmed the overall and breast cancer–specific mortality associations with the four comorbidities (data not shown). Limitations include availability of a small group of comorbidities and information on comorbidities (except previous cancer) based entirely on self-report. Better understanding of overall and breast-cancer specific mortality in relation to the individual comorbidities, as well as a combination of comorbidities such as the Charlson Comorbidity Index, diagnosed before as well as after (35–37) breast cancer diagnosis, will be needed. Our cancer registry information on radiotherapy and chemotherapy for breast cancer was limited to the first course of treatment. Although we had some information on treatment for the comorbidities, this

Published OnlineFirst November 25, 2014; DOI: 10.1158/1055-9965.EPI-14-1140

was crude and lacked details such as specific diabetic medications or the reasons why some patients were not treated. Collection of information on specific diabetic medications (e.g., metformin, sulfonylurea) will help inform the extent to which specific treatments may influence outcomes in patients with breast cancer (38, 39), a topic of immense interest.

In summary, we found that the risk of breast cancer–specific mortality was significantly increased among women with a history of diabetes or myocardial infarction. Stratified analyses showed that risk patterns for diabetes and myocardial infarction varied significantly by receipt of radiotherapy and chemotherapy and that risk was higher among patients with a previous cancer. With the growing number of breast cancer survivors worldwide, confirmation of these results is needed to better understand how comorbidities may adversely affect treatment decisions and ultimately outcome.

Disclosure of Potential Conflicts of Interest

S.L. Gomez reports receiving a commercial research grant from Genentech. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, the California Department of Health Services, the National Cancer Institute, or the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

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Acknowledgments

The authors thank all the study participants for their contributions in the six California-based studies, Juan Yang and Rita Leung at CPIC for their analytic support, and Janise M. Roh at KPNC for her administrative support.

Grant Support

This work was supported by grants 16ZB-8001 (to A.H. Wu, R. Sposto, C.-C. Tseng, and C. Vigen), 16ZB-8002 (to S.L. Gomez, E.M. John, T.H.M. Keegan, A.W. Kurian, and S. Shariff-Marco), 16ZB-8003 (to L. Bernstein, Y. Lu, and J. Sullivan-Halley), 16ZB-8004 (to M.L. Kwan, B.J. Caan, and V.S. Lee), and 16ZB-8005 (to I. Cheng) from the California Breast Cancer Research Program. The AABCS was supported by the California Breast Research Program (CBCRP) grants 1RB-0287, 3PB-0120, and 5PB-0018 (to A.H. Wu and C.-C. Tseng). The SFBCS was supported by National Cancer Institute grants R01 CA63446 and R01 CA77305, by the U.S. Department of Defense (DOD) grant DAMD17-96-1-6071, and by the CBCRP grants 4JB-1106 and 7PB-0068 (to E.M. John). The Women's CARE Study was funded by the National Institute of Child Health and Human Development (NICHD), through a contract with USC (N01-HD-3-3175), and the CTS was funded by the California Breast Cancer Act of 1993; National Cancer Institute grants (R01 CA77398 and K05 CA136967 to L. Bernstein); and the California Breast Cancer Research Fund (contract 97-10500; to L. Bernstein, J. Sullivan-Halley, and Y. Lu). The Multiethnic Cohort Study was supported by National Cancer Institute grants R01 CA54281, R37CA54281, and UM1 CA164973 (to I. Cheng). The LACE Study is supported by National Cancer Institute grant R01 CA129059 (to B.J. Caan and M.L. Kwan). Clinical and tumor characteristics and mortality data were obtained from the CCR, also part of the National Cancer Institute's Division of Cancer Prevention and Control Surveillance, Epidemiology, and End Results Program, under contract number N01CN25403. The collection of cancer incidence data used in this study was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN26120100035C awarded to the University of Southern California, and contract HHSN26120100034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #1U58 DP000807-01 awarded to the Public Health Institute.

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Received October 6, 2014; revised November 14, 2014; accepted November 17, 2014; published OnlineFirst November 25, 2014.

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Published OnlineFirst November 25, 2014; DOI: 10.1158/1055-9965.EPI-14-1140

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Published OnlineFirst November 25, 2014; DOI: 10.1158/1055-9965.EPI-14-1140

Cancer Epidemiology, Biomarkers & Prevention

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Diabetes and Other Comorbidities in Breast Cancer Survival by Race/Ethnicity: The California Breast Cancer Survivorship Consortium (CBCSC)

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Cancer Epidemiol Biomarkers Prev 2015;24:361-368. Published OnlineFirst November 25, 2014.