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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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Abstract

Background—The role of comorbidities in survival of breast cancer patients has not been well studied, particularly in non-white 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 hazards ratios (HR) and 95% confidence intervals (CI) for overall and breast cancer-specific mortality associated with previous cancer, diabetes, high blood pressure (HBP), and myocardial infarction (MI).

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 MI (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 radiation 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 interaction= 0.03). A similar pattern was found for MI by radiation and chemotherapy (P interaction=0.09).

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Conclusion—These results may inform future treatment guidelines for breast cancer patients with a history of diabetes or MI.

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.

Keywords

race/ethnicity; diabetes; myocardial infarction; survival; treatment; tumor characteristics; lifestyle factors

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 breast cancer patients had one or more comorbidities near the time of diagnosis (1), and breast cancer patients 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 breast cancer patients 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) (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 (CBCSC)

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 studies of breast cancer [the Asian American Breast Cancer Study (AABCS) (6); the Women's Contraceptive and Reproductive Experiences study (CARE) (7); and the San Francisco Bay Area Breast Cancer Study (SFBCS) (8)], one breast cancer survivor cohort [the Life after Cancer Epidemiology (LACE) Study (9)], and one cohort study [the California Teachers Study (CTS) (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 (MI) or heart attack] from questionnaires. Questions on comorbidities were similar in the three case-control studies, which conducted in-person interviews on average 3–18 months after breast cancer diagnosis thatqueried 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 MI 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 which asked about diabetes, MI, 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 if they were ever told by a doctor or other health professional of having diabetes, HBP, or MI and when they were first told. Only conditions that occurred prior to the date of breast cancer diagnosis were considered.

CBCSC participants were linked to the CCR (5) to obtain information on previous cancer (excluding non-melanoma skin cancer), AJCC stage, estrogen receptor (ER) and progesterone receptor (PR) status, nodal positivity, grade, tumor size, surgery type, chemotherapy, hormonal therapy, radiation therapy, 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 hazard ratios (HRs) and 95% confidence intervals (CIs) 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 (U.S. 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 radiation. Of the 10,212 breast cancer patients 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 MI). We conducted analyses mutually adjusted for previous cancer, diabetes, HBP, and MI 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, MI) and mortality outcomes by menopausal status, BMI, and AJCC stage and by first course of breast cancer treatment (type of breast surgery, radiation 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 breast cancer patients with each type of comorbidity. The prevalence of HBP was high (27.7%), followed by previous cancer (6.8%), diabetes (5.5%), and MI (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 radiation therapy.

History of previous cancer, diabetes, HBP and MI were 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 MI (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 P's <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 interaction=0.01). History of MI was associated with overall (HR=1.44, 95% CI=1.06–1.95) and breast cancer-specific (HR=1.82, 95% CI=1.04–3.16) mortality in non-Latina Whites; non-significant 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. Ppatients

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 6–14 years (HR=1.45, 95% CI=0.92–2.27), and lowest among those who had diabetes for ≤5 years prior to breast cancer diagnosis (HR=1.13, 95% CI=0.76–1.69) compared to those without diabetes. Breast cancer patients, 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 MI.

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 MI, 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 MI (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, breast cancer 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 MI 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 MI was not statistically significant (HR=1.79, 95% CI=0.64–4.96). The mortality patterns associated with diabetes, HBP, and MI 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, radiation, chemotherapy). The mortality patterns associated with MI 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 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 radiation 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 to breast cancer patients who had no diabetes with corresponding treatments (Table 5). A similar pattern of results was observed for diabetes and overall mortality when treatment with radiation and chemotherapy was considered. There were no increased risks of overall or breast cancer-specific mortality in association with history of MI for those treated with both chemotherapy and radiation. However, patients with MI, who received either radiation 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 breast cancer patients followed an average of 9.8 ± 3.5 years, patients with a history of diabetes or MI 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 radiation or chemotherapy. The association was strongest for patients who reported no treatment for diabetes. Our findings on previous cancer in combination with diabetes and MI suggest synergistic effects of these conditions. These results emphasize that the survival of breast cancer patients may be compromised because of under-treatment 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 non-registry 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 radiation 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 were treated with chemotherapy or radiation may be healthier than their counterparts who were not offered comparable therapy. Radiation, chemotherapy, and other treatments are also less likely to be offered to breast cancer patients 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 breast cancer patients with a history of MI experienced increased overall and breast cancer-specific mortality irrespective of a prior cancer, but risks were higher among those who did not receive radiation or chemotherapy. Breast cancer patients with a history of cardio-vascular 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, non-cancer 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 MI may be related to concern that specific chemotherapy such as anthracyclines may have long-term cardiac toxicity in breast cancer patients, 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 to 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 radiation 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 which 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 radiation and chemotherapy for breast cancer was limited to the first course of treatment. While we had some information on treatment for the comorbidities, this 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 breast cancer patients (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 MI. Stratified analyses showed that risk patterns for diabetes and MI varied significantly by receipt of radiation 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 in order to better understand how comorbidities may adversely affect treatment decisions and ultimately outcome.

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Table. 1

Characteristics of breast cancer patients with a history of comorbidities[1], California Breast Cancer Survivorship Consortium, diagnoses 1993–2007

	Previous cancer		Diabetes		High blood pressure or hypertension		Myocardial Infarction	
	Total	Yes (%)	Total	Yes (%)	Total	Yes (%)	Total	Yes (%)
	8952	605(6.8)	8946	489(5.5)	8952	2479(27.7)	8108	136(1.7)
Age (years)								
<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	1752 (19.6)	72 (11.9)	1751 (19.6)	72 (14.7)	1752 (19.6)	273 (11.0)	1491 (18.4)	13 (9.6)
50–59	2662 (29.7)	147 (24.3)	2659 (29.7)	125 (25.6)	2662 (29.7)	682 (27.5)	2435 (30.0)	23 (16.9)
60–69	2229 (24.9)	163 (26.9)	2229 (24.9)	163 (33.3)	2229 (24.9)	751 (30.3)	2054 (25.3)	34 (25.0)
≥70	1798 (20.1)	210 (34.7)	1796 (20.1)	114 (23.3)	1798 (20.1)	741 (29.9)	1672 (20.6)	66 (48.5)
P value		<0.0001		<.0001		<0.0001		<0.0001
Race/ethnicity								
Non-Latina White	5683 (63.5)	455 (75.2)	5682 (63.5)	171 (35.0)	5683 (63.5)	1391 (56.1)	5550 (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	1354 (15.1)	48 (7.9)	1354 (15.1)	109 (22.3)	1354 (15.1)	392 (15.8)	1354 (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 value		<0.0001		<0.0001		<0.0001		0.02
Neighborhood socioeconomic status(SES)[2]								
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	1105 (12.3)	70 (11.6)	1103 (12.3)	104 (21.3)	1105 (12.3)	372 (15.0)	969 (12.0)	17 (12.5)
Middle	1669 (18.6)	133 (22.0)	1668 (18.6)	116 (23.7)	1669 (18.6)	492 (19.8)	1492 (18.4)	35 (25.7)
Higher-middle	2314 (25.8)	142 (23.5)	2313 (25.9)	99 (20.2)	2314 (25.8)	615 (24.8)	2096 (25.9)	34 (25.0)
Highest	3049 (34.1)	204 (33.7)	3048 (34.1)	99 (20.2)	3049 (34.1)	724 (29.2)	2783 (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 value		0.25		<0.0001		<0.0001		0.27
Tumor stage (American Joint Committee on Cancer, AJCC)								
I	4381 (48.9)	328 (54.2)	4378 (48.9)	202 (41.3)	4381 (48.9)	1214 (49.0)	4013 (49.5)	79 (58.1)
II	3674 (41.0)	217 (35.9)	3671 (41.0)	225 (46.0)	3674 (41.0)	1029 (41.5)	3290 (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 value		0.014		0.024		0.32		0.56
	Previous cancer		Diabetes		High blood pressure		Myocardial Infarction	
	Total	Yes (%)	Total	Yes (%)	Total	Yes (%)	Total	Yes (%)
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	3817 (42.6)	241 (39.8)	3815 (42.6)	230 (47)	3817 (42.6)	1108 (44.7)	3457 (42.6)	71 (52.2)
Breast conserving surgery	4982 (55.7)	345 (57.0)	4978 (55.6)	246 (50.3)	4982 (55.7)	1326 (53.5)	4513 (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 value		0.006		0.002		0.14		0.12
Chemotherapy								
No	4898 (54.7)	392 (64.8)	4894 (54.7)	284 (58.1)	4898 (54.7)	1545 (62.3)	4507 (55.6)	102 (75.0)
Yes	3910 (43.7)	203 (33.6)	3908 (43.7)	197 (40.3)	3910 (43.7)	905 (36.5)	3470 (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 value		<0.0001		0.38		<0.0001		<0.0001
Radiation therapy								
No	4187 (46.8)	307 (50.7)	4185 (46.8)	255 (52.1)	4187 (46.8)	1220 (49.2)	3848 (47.5)	77 (56.6)
Yes	4765 (53.2)	298 (49.3)	4761 (53.2)	234 (47.9)	4765 (53.2)	1259 (50.8)	4260 (52.5)	59 (43.4)
P value		0.04		0.02		0.013		0.08
Body mass index (BMI, kg/m^2)								
<25.0	4657 (52.0)	336 (55.5)	4534 (50.7)	120 (24.5)	4534 (50.6)	844 (34.0)	4278 (52.8)	57 (41.9)
25.0 to ≤29.9	2469 (27.6)	150 (24.8)	2589 (28.9)	133 (27.2)	2592 (29.0)	832 (33.6)	2301 (28.4)	41 (30.1)
30.0 to ≤34.9	1032 (11.5)	67 (11.1)	1032 (11.5)	135 (27.6)	1032 (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 value		0.22		<.0001		<.0001		<.0001

[1] No and unknown condition are not shown for the five comorbidities.

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

Table 2

Race/ethnicity-specific associations between history of comorbidities and overall mortality and breast cancer (BC)-specific mortality, California Breast Cancer Survivorship Consortium, diagnoses 1993–2007

	Previous Cancer		Diabetes		High blood pressure 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[1]	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[2]	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[2]	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[2]	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[2]	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)[§]	0.52 (0.33–0.81)[#]	2.01 (0.69–5.82)	1.10 (0.15–8.33)

[1] Adjusted for race/ethnicity, age, stage (AJCC)), hormone receptor status, nodal involvement, grade, tumor size, surgery type, chemotherapy, radiation therapy, prior cancer, body mass index, education, neighborhood SES, nativity, marital status, menopausal status, age at first birth, smoking, and alcohol consumption

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

[§] p-value for interaction of Non-Latina White vs Asian American with hypertension for overall mortality = 0.03.

[#] p-value for interaction of Non-Latina White vs Asian American with hypertension for breast cancer-specific mortality = 0.01.

Table 3

Overall mortality and breast cancer-specific mortality in relation to diabetes, hypertension, and myocardial infarction (MI) by timing and treatment for comorbidity, and by history of previous cancer, California Breast Cancer Survivorship Consortium, diagnoses 1993–2007

	Diabetes		High blood pressure or hypertension		Myocardial Infarction	
	Overall HR[1] (95%CI)	**Breast cancer-specific HR[1] (95 %CI)**	**Overall HR[1] (95%CI)**	**Breast cancer-specific HR[1] (95%CI)**	**Overall HR[1] (95%CI)**	**Breast cancer-specific HR[1] (95%CI)**
Duration of comorbidity prior to breast cancer diagnosis						
No comorbidity	1.00	1.00	1.00	1.00	1.00	1.00
Yes comorbidity ≤5yr	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)[2]	1.41 (0.62–3.23)[2]
Yes comorbidity 6 –14 yr	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 ≥15yr	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)		
Previous Cancer (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)

[1] Adjusted for race/ethnicity, age, stage (American Joint Committee on Cancer, AJCC), hormone receptor status, nodal involvement, grade, tumor size, surgery type, chemotherapy, radiation therapy, prior cancer, body mass index, education, neighborhood SES, nativity, marital status, menopausal status, age at first birth, smoking, and alcohol consumption

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

Table 4

Comorbidities and overall mortality and breast cancer-specific mortality stratified by type of breast surgery[1], California Breast Cancer Survivorship Consortium, diagnoses 1993–2007

	Overall mortality						Breast cancer-specific mortality					
	Mastectomy			Breast conserving surgery			Mastectomy			Breast conserving surgery		
	Death/ No Event	HR[2]	95% CI	Death/ No Event	HR[2]	95% CI	Death/ No Event	HR[2]	95% CI	Death/ No Event	HR[2]	95% CI
Diabetes[3]												
No	954/2543	1.00		888/3783	1.00		558/2939	1.00		401/4270	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
High blood pressure or hypertension[3]												
No	712/1967	1.00		602/3034	1.00		455/2224	1.00		305/3331	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	132/1198	1.12	0.89–1.41
P interaction						0.02						0.06
Myocardial infarction[3]												
No	954/2393	1.00		862/3567	1.00		544/2803	1.00		380/4049	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	1000/2576	1.00		891/3746	1.00		581/2995	1.00		401/4236	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

[1] Excluded patients who had no surgery (n=141) or other type of surgery (n=12).

[2] Adjusted for race/ethnicity, age, stage (American Joint Committee on Cancer, AJCC), hormone receptor status, nodal involvement, grade, tumor size, radiation therapy, chemotherapy, prior cancer (except in the analysis on previous cancer), body mass index, education, neighborhood SES, nativity, marital status, menopausal status, age at first birth, smoking, and alcohol consumption

[3] Analyses on diabetes, high blood pressure or hypertension, myocardial infarction were based on 8797, 8905, and 8062 patients, respectively, because of some missing data.

Table 5

Comorbidities and overall mortality and breast cancer-specific mortality stratified by radiation and chemotherapy, California Breast Cancer Survivorship Consortium, diagnoses 1993–2007

	Overall mortality						Breast cancer-specific mortality					
	Radiation and Chemotherapy						Radiation and Chemotherapy					
	Yes to both		Yes to either		No to both		Yes to both		Yes to either		No to both	
	Death/ No Event	HR[1] 95% CI	Death/ No Event	HR[1] 95% CI	Death/ No Event	HR[1] 95% CI	Death/ No Event	HR[1] 95% CI	Death/ No Event	HR[1] 95% CI	Death/ No Event	HR[1] 95% CI
Diabetes[2]												
No	513/1601	1.00	801/3068	1.00	605/1708	1.00	392/1722	1.0	423/3446	1.0	197/2116	1.00
Yes	39/62	1.56	107/122	1.73	75/84	2.34	22/79	1.13	45/184	1.49	28/131	2.11
		1.07–2.26		1.38–2.17		1.77–3.08		0.70–1.84		1.05–2.11		1.32–3.36
P interaction				0.62		0.04				0.47		0.03
High blood pressure or hypertension[2]												
No	402/1325	1.00	571/2427	1.00	398/1292	1.00	316/1411	1.00	337/2661	1.00	147/1543	1.00
Yes	156/349	1.03	350/804	1.22	294/526	1.29	99/406	0.91	136/1018	0.92	81/739	1.06
		0.83–1.28		1.06–1.42		1.09–1.54		0.70–1.18		0.74–1.15		0.76–1.46
P interaction				0.18		0.08				0.93		0.40
Myocardial infarction[2]												
No	478/1449	1.00	804/2921	1.00	611/1637	1.00	360/1567	1.00	419/3306	1.00	199/2049	1.00
Yes	4/11	0.73	26/36	1.95	37/22	1.64	2/13	0.53	11/51	2.45	11/48	2.40
		0.26–2.05		1.29–2.94		1.14–2.36		0.12–2.27		1.31–4.59		1.20–4.79
P interaction				0.05		0.11				0.07		0.09
Previous cancer												
No	530/1614	1.00	836/3050	1.00	608/1709	1.00	395/1749	1.0	434/3452	1.00	214/2103	1.00
Yes	34/74	1.18	92/193	1.26	88/124	1.48	23/85	1.10	41/244	1.31	15/197	0.84
		0.81–1.72		1.00–1.57		1.16–1.88		0.70–1.74		0.93–1.85		0.48–1.46
P interaction				0.26		0.14				0.34		0.50

[1] Adjusted for race/ethnicity, age, stage (American Joint Committee on Cancer, AJCC), hormone receptor status, nodal involvement, grade, tumor size, surgery type, prior cancer (except in the analysis or previous cancer), body mass index, education, neighborhood SES, nativity, marital status, menopausal status, age at first birth, smoking, and alcohol consumption

[2] Analyses on diabetes, high blood pressure or hypertension, myocardial infarction were based on 8785, 8894, and 8036 patients, respectively, because of some missing data.