Title
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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 patients with breast cancer 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 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; Pinteraction = 0.03). A similar pattern was found for myocardial infarction by radiotherapy and chemotherapy (Pinteraction = 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.

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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...
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. HBP 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 Latinos and Asian Americans, but with breast cancer–specific mortality only among Latinos (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 < 0.05] and suggestive for breast cancer–specific mortality 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 (Pinteraction = 0.01). History of myocardial infarction was associated with overall (HR, 1.44; 95% CI, 1.06–1.95) and breast
Diabetes and Other Comorbidities in Breast Cancer Survival

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.

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Yes (%)</th>
<th>Diabetes</th>
<th>Yes (%)</th>
<th>HBP or hypertension</th>
<th>Yes (%)</th>
<th>Myocardial infarction</th>
<th>Yes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>4,657 (52.0)</td>
<td>336 (55.5)</td>
<td>4,534 (50.7)</td>
<td>120 (24.5)</td>
<td>4,534 (50.6)</td>
<td>844 (34.0)</td>
<td>4,278 (52.8)</td>
<td>57 (41.9)</td>
</tr>
<tr>
<td>25.0 to &lt;29.9</td>
<td>2,469 (26.7)</td>
<td>150 (24.8)</td>
<td>2,589 (28.9)</td>
<td>133 (27.2)</td>
<td>2,592 (29.0)</td>
<td>832 (33.6)</td>
<td>2,301 (28.4)</td>
<td>41 (30.3)</td>
</tr>
<tr>
<td>30.0 to &lt;34.9</td>
<td>1,032 (11.5)</td>
<td>67 (11.1)</td>
<td>1,032 (11.5)</td>
<td>135 (27.6)</td>
<td>1,032 (11.5)</td>
<td>473 (19.1)</td>
<td>842 (10.4)</td>
<td>22 (16.2)</td>
</tr>
<tr>
<td>≥35.0</td>
<td>562 (6.3)</td>
<td>32 (5.3)</td>
<td>562 (6.3)</td>
<td>88 (18.0)</td>
<td>562 (6.3)</td>
<td>268 (10.8)</td>
<td>465 (5.7)</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>232 (2.6)</td>
<td>20 (3.3)</td>
<td>232 (2.6)</td>
<td>15 (2.7)</td>
<td>232 (2.6)</td>
<td>62 (2.5)</td>
<td>222 (2.7)</td>
<td>4 (2.9)</td>
</tr>
</tbody>
</table>

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

*Neighborhood SES index, which is a composite measure of 7 Census indicator variables.

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

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall</th>
<th>BC-specific</th>
<th>Diabetes</th>
<th>HBP or hypertension</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>No comorbidity</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes comorbidity ≤5 y</td>
<td>1.54 (1.17–2.02)</td>
<td>1.13 (0.76–1.69)</td>
<td>1.06 (0.89–1.27)</td>
<td>0.91 (0.71–1.16)</td>
<td>1.34 (0.83–2.16)</td>
</tr>
<tr>
<td>Yes comorbidity 6–14 y</td>
<td>2.02 (1.51–2.71)</td>
<td>1.45 (0.92–2.27)</td>
<td>1.24 (1.03–1.49)</td>
<td>1.03 (0.79–1.33)</td>
<td>1.93 (1.37–2.71)</td>
</tr>
<tr>
<td>Yes comorbidity ≥15 y</td>
<td>1.88 (1.38–2.57)</td>
<td>1.81 (1.17–2.81)</td>
<td>1.18 (0.97–1.44)</td>
<td>0.93 (0.70–1.24)</td>
<td>2.00 (0.87–4.58)</td>
</tr>
<tr>
<td>Treated for comorbidity</td>
<td>No comorbidity</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes comorbidity ≤5 y</td>
<td>1.83 (1.36–2.81)</td>
<td>2.12 (1.25–3.63)</td>
<td>0.89 (0.58–1.36)</td>
<td>0.80 (0.48–1.32)</td>
<td>Not available</td>
</tr>
<tr>
<td>Yes comorbidity 6–14 y</td>
<td>1.69 (1.38–2.07)</td>
<td>1.13 (0.82–1.55)</td>
<td>1.13 (0.94–1.35)</td>
<td>0.95 (0.75–1.19)</td>
<td>Not available</td>
</tr>
<tr>
<td>Yes comorbidity ≥15 y</td>
<td>2.06 (1.62–2.67)</td>
<td>2.02 (1.39–2.93)</td>
<td>1.24 (1.11–1.39)</td>
<td>0.96 (0.80–1.16)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PC, previous cancer.

1Adjusted 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.

2Duration 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.

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

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall</th>
<th>Breast cancer–specific</th>
<th>HBP or hypertension</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>No comorbidity</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes comorbidity ≤5 y</td>
<td>1.54 (1.17–2.02)</td>
<td>1.13 (0.76–1.69)</td>
<td>1.06 (0.89–1.27)</td>
<td>0.91 (0.71–1.16)</td>
</tr>
<tr>
<td>Yes comorbidity 6–14 y</td>
<td>2.02 (1.51–2.71)</td>
<td>1.45 (0.92–2.27)</td>
<td>1.24 (1.03–1.49)</td>
<td>1.03 (0.79–1.33)</td>
</tr>
<tr>
<td>Yes comorbidity ≥15 y</td>
<td>1.88 (1.38–2.57)</td>
<td>1.81 (1.17–2.81)</td>
<td>1.18 (0.97–1.44)</td>
<td>0.93 (0.70–1.24)</td>
</tr>
</tbody>
</table>

Abbreviation: PC, previous cancer.

1Adjusted 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.

2Duration 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.
Diabetes, previous cancer, and other comorbidities show an increased risk of breast cancer and mortality. 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 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 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.

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).

Table 4. Comorbidities and overall mortality and breast cancer-specific mortality stratified by type of breast surgery, CBSCC, diagnoses 1993–2007

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall mortality</th>
<th>Breast cancer-specific mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td>Death/no event HR (95% CI)</td>
<td>Death/no event HR (95% CI)</td>
</tr>
<tr>
<td>No</td>
<td>954/2,545 1.00</td>
<td>558/2,939 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>120/110 2.01 (1.62–2.50)</td>
<td>56/174 1.60 (1.17–2.18)</td>
</tr>
<tr>
<td>P_interaction</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

HBP or hypertension

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall mortality</th>
<th>Breast cancer-specific mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>712/1,967 1.00</td>
<td>455/2,224 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>380/728 1.04 (0.90–1.20)</td>
<td>163/945 0.80 (0.66–0.98)</td>
</tr>
<tr>
<td>P_interaction</td>
<td>0.02</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Myocardial infarction

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall mortality</th>
<th>Breast cancer-specific mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>954/2,938 1.00</td>
<td>544/2,803 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>38/33 1.44 (1.02–2.03)</td>
<td>15/56 1.33 (0.89–2.63)</td>
</tr>
<tr>
<td>P_interaction</td>
<td>0.80</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Previous cancer

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall mortality</th>
<th>Breast cancer-specific mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1,000/2,576 1.00</td>
<td>581/2,995 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>100/141 1.34 (1.08–1.66)</td>
<td>41/200 1.12 (0.80–1.57)</td>
</tr>
<tr>
<td>P_interaction</td>
<td>0.81</td>
<td>0.95</td>
</tr>
</tbody>
</table>

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

*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.

*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.

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

<table>
<thead>
<tr>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes to both</td>
</tr>
<tr>
<td>39/62</td>
</tr>
<tr>
<td>107/122</td>
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<tr>
<td>75/84</td>
</tr>
<tr>
<td>22/79</td>
</tr>
<tr>
<td>45/184</td>
</tr>
<tr>
<td>28/131</td>
</tr>
</tbody>
</table>

| Death/no event | HR (95% CI) |
| 392/1222 | 10 |
| 423/3446 | 1.0 |
| 45/84 | 1.49 (1.05–2.11) |
| 217/156 | 1.0 |
| 28/131 | 2.11 (1.32–3.36) |

<table>
<thead>
<tr>
<th>Myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes to both</td>
</tr>
<tr>
<td>4/11</td>
</tr>
<tr>
<td>37/22</td>
</tr>
<tr>
<td>11/51</td>
</tr>
<tr>
<td>11/48</td>
</tr>
</tbody>
</table>

| Death/no event | HR (95% CI) |
| 360/1567 | 1.00 |
| 419/3306 | 1.00 |
| 11/51 | 2.43 (1.31–4.59) |
| 11/48 | 2.40 (1.20–4.79) |

<table>
<thead>
<tr>
<th>Previous cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes to both</td>
</tr>
<tr>
<td>34/74</td>
</tr>
<tr>
<td>88/124</td>
</tr>
<tr>
<td>41/244</td>
</tr>
<tr>
<td>15/197</td>
</tr>
</tbody>
</table>

| Death/no event | HR (95% CI) |
| 395/1494 | 10 |
| 434/4562 | 1.00 |
| 41/244 | 1.31 (0.93–1.85) |
| 15/197 | 0.84 (0.48–1.46) |

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

*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.

Our findings of an association of HBP with overall but not breast cancer-specific mortality are consistent with studies that asked very similar questions on comorbidities and information on comorbidities (except previous cancer) based studies (3, 4) may be lower (21–22). Thus, our findings are consistent with studies among women with breast cancer with a history of myocardial infarction who showed worse survival in the absence of radiotherapy and chemotherapy. Compared with breast cancer patients who had breast-conserving surgery and chemotherapy, women with breast cancer with a history of myocardial infarction may have long-term cardiac toxicity in patients with breast cancer, particularly in older patients (33–35). Patients with breast cancer with a history of myocardial infarction 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 breast-conserving surgery may have adverse effects on cardiac function (31).
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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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.H. Wu, M.L. Kwan, B.J. Caan, C.-C. Tseng, R. Sposto, C. Vigen
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.H. Wu, M.L. Kwan, Y. Lu, S.L. Gomez, S. Shariff-Marco, C. Vigen
Study supervision: A.H. Wu, S.L. Gomez, L. Bernstein

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References
22. Houterman S, Janssen-Heijnen ML, Verheij CD, Louwman WJ, Vreugden- 
20. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular 
24. Griggs JJ, Culakova E, Sorbero ME, Poniewierski MS, Wolff DA, Crawford J, 
16. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der 
15. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. The impact 
21. Land LH, Dalton SO, Jensen MB, Ewertz M. Impact of comorbidity on 
20. 403.

13. Schmitz KH, Prosnitz RG, Schwartz AI, Carver JR. Prospective surveillance 
32. Azim HA Jr, de Azambuja E, Colozza M, Bines J, Piccart MJ. Long-term toxic 
37. Kiderlen M, de Glas NA, Bastiaannet E, Engels CC, van de Water W, de 
38. Qiu H, Rhoads GG, Berlin JA, Marcella SW, Demissie K. Initial met- 
30. Darby SC, Ewertz M, McCage P, Bennet AM, Blom-Goldman U, Bronnum D, 
34. Holmes MD, Chen WY. Hiding in plain view: the potential for commonly 
33. Schmitz KH, Prosnitz RG, Schwartz AL, Carver JR. Prospective surveillance 
25. – 69.

11. Yost K, Perkins C, Cohen R, Morris C, Wright W. Socioeconomic status and 
10. 421.

12. Arcidiacono B, Iritiano S, Nobera A, Possidente K, Nevolo MT, Ventura V, 
et al. Insulin resistance and cancer risk: an overview of the pathogenetic 

NP, et al. Reducing the weight of cancer: mechanistic targets for breaking 
the obesity-carcinogenesis link. Best Pract Res Clin Endocrinol Metab 

with stage I-II breast cancer at a large academic medical center in metro-

15. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der 

16. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der 

and comorbidity in postmenopausal breast cancer patients aged 55 years 

Medical comorbidities predict mortality in women with a history of early 

breast cancer survival: a report from the Shanghai Breast Cancer Survival 

20. Patnaik RJ, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular 
disease competes with breast cancer as the leading cause of death for 
older females diagnosed with breast cancer: a retrospective cohort study. 
Breast Cancer Res 2011;13:R64.

21. Land LH, Dalton SO, Jensen MB, Ewertz M. Impact of comorbidity on 
mortality: a cohort study of 62,591 Danish women diagnosed with early 

22. Houterman S, Janssen-Heijnen ML, Veerheijd CJ, Louwman WJ, Veugden-

23. Smokowski TP, Fang S, Horta-Bageiri GN, Giordano SH. Impact of diabets 
mellitus on complications and outcomes of adjuvant chemotherapy in 

24. Grigg JJ, Calakova E, Sorbero ME, Ponomierski MS, Wolff DA, Crawford J, 
et al. Social and racial differences in selection of breast cancer adjuvant 

Patterns and correlates of adjuvant radiotherapy receipt after lumpectomy 

of radiotherapy and of differences in the extent of surgery for early breast 
cancer on local recurrence and 15-year survival: an overview of the 

Early discontinuation and non-adherence to adjuvant hormonal therapy 
are associated with increased mortality in women with breast cancer. Breast 

28. Vinh-Hung V, Venschaeghen C. Breast-conserving surgery with or without 
radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recur-

Effect of radiotherapy after breast-conserving surgery on 10-year recur-

30. Darby SC, Ewertz M, McCage P, Bennet AM, Blom-Goldman U, Bronnum D, 
et al. Risk of ischemic heart disease in women after radiotherapy for 

DL, et al. Patterns and predictors of breast cancer chemotherapy use in 

32. Azim HA Jr, de Azambuja E, Colozza M, Bines J, Piccart MJ. Long-term toxic 
effects of adjuvant chemotherapy in breast cancer. Ann Oncol 2011;22: 
1939–47.

33. Schmitz KH, Prosnitz RG, Schwartz AI, Carver JR. Prospective surveillance 
and management of cardiac toxicity and health in breast cancer survivors. 

34. Holmes MD, Chen WY. Hiding in plain view: the potential for commonly 
used drugs to reduce breast cancer mortality. Breast Cancer Res 2012;14: 
216.

comorbidities and all-cause mortality among 5-year survivors of Stage I 
and II breast cancer diagnosed at age 65 or older: a prospective-matched 

Comorbidities and cardiovascular disease risk in older breast cancer 

37. Kiderlen M, de Glas NA, Bastiaannet E, Engels CC, van de Water W, de 
mortality in elderly breast cancer patients: a FOCUS study analysis. Ann 
Oncol 2013;24:3011–6.

38. Qiu H, Rhoads GC, Berlin JA, Marcella SW, Demissie K. Initial met- 
formin or sulphonylurea exposure and cancer occurrence among 
patients with type 2 diabetes mellitus. Diabetes Obes Metab 2013;15: 
349–57.


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

Anna H. Wu, Allison W. Kurian, Marilyn L. Kwan, et al.


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