The Impact of Diabetes on Breast Cancer Treatments and Outcomes: A Population-Based Study

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OBJECTIVE

Women with breast cancer and diabetes face worse outcomes than those with breast cancer without diabetes; however, the contribution of comorbidity to these disparities remains unclear. We evaluated the impact of diabetes on receipt of cancer treatments as well as mortality while accounting for other comorbidities.

RESEARCH DESIGN AND METHODS

Ontario administrative databases were used to compare the rate of receipt of breast cancer treatments between women with and without diabetes. We also performed adjusted cause-specific hazard models to account for comorbidities when evaluating differences in treatments received and mortality outcomes between the two groups.

RESULTS

Women with diabetes and stage III breast cancer were slightly less likely to receive chemotherapy (relative risk [RR] 0.93 [95% CI 0.89–0.97]), although this difference was not significant when we adjusted for comorbidities (adjusted hazard ratio [aHR] 1.03 [95% CI 0.93–1.13]). We saw similar trends for receipt of guideline-adherent radiotherapy (RR 0.97 [0.95–0.99], aHR 0.98 [0.94–1.02]). All-cause mortality was increased in women with diabetes after adjusting for comorbidities (aHR 1.16 [1.06–1.27]), but breast cancer–specific mortality was not increased overall. Women with a longer duration of diabetes and those with preexisting cardiovascular disease had increased all-cause and cancer-specific mortality.

CONCLUSIONS

Although cancer treatments received were similar between women with and without diabetes, breast cancer–specific mortality remains higher among women with diabetes who have longer diabetes duration or preexisting cardiovascular disease. This study uncovers new information about key risk factors for poorer prognosis in women with diabetes and breast cancer.

Diabetes affects up to one-third of patients with breast cancer (1), and evidence shows that women with diabetes have a 40% higher risk of mortality after breast cancer than women without diabetes (1–4). Diabetes not only increases noncancer mortality as a result of diabetes-related complications but also affects breast cancer–specific mortality (5). Women with diabetes may face poorer breast cancer prognosis because of estrogenic effects of obesity or metabolic factors such as the growth-promoting influence of hyperinsulinemia and insulin resistance that can lead to more aggressive disease (6–8). Cancer prognosis also may be affected by health care disparities in patients with diabetes. Indeed, studies show that women with diabetes have lower

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breast cancer screening rates (9) and present with more advanced disease than women without diabetes (1,10,11).

Women with diabetes and other comorbidities receive less aggressive cancer treatments, particularly with regard to chemotherapy (1,5,12–14). However, studies in settings with potential access barriers to care did not account for the copresence of cardiovascular disease. Because of the known cardiotoxic effects of certain chemotherapy regimens, physicians may elect for more conservative chemotherapy in patients with cardiovascular disease. Because cardiovascular risk is higher in women with diabetes, to what extent the presence of cardiovascular disease beyond diabetes affects a physician's decision making when choosing a cancer treatment regimen is unclear. Radiotherapy (for left-sided disease) is an important treatment for breast cancer with a potential for long-term cardiotoxicity (15); thus, it may also be avoided more often in women with diabetes.

Although evidence suggests that the presence of diabetes portends a poorer prognosis of breast cancer, the contribution of cancer treatment disparities in relation to other factors remains unclear. The impact of diabetes on breast cancer mortality may be especially salient if there is lower adherence to guideline-recommended treatments in those who would benefit most. In this context, we used large population-based health databases to investigate whether the presence of diabetes among patients with breast cancer leads to differences in guideline-adherent chemotherapy and radiotherapy treatment. We also evaluated the impact of diabetes on all-cause and breast cancer–specific mortality while accounting for treatments received and the presence of comorbidities.

RESEARCH DESIGN AND METHODS

Study Design and Data Sources

This retrospective cohort study used linked population-based health databases from Ontario, Canada, which provides universal health coverage for its >12 million residents. These data sets were linked by using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). The following databases were used: Ontario Cancer Registry (OCR), Cancer Care Ontario (CCO) staging data, the validated Ontario Diabetes Database (ODD), Ontario Health Insurance Plan (OHIP) billing claims database, New Drug Funding Plan database, Canadian Institute for Health Information (CIHI) Hospital Discharge Abstract Database, National Ambulatory Care Reporting System, Same Day Surgery database, Registered Persons Database (RPDB), and Office of the Registrar General Death Data. The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada.

Study Population

The study population included women age ≥20 years with stage I–III breast cancer diagnosed between 1 January 2007 and 31 December 2012. Women were identified from the OCR on the basis of ICD-9 code 174, and we included only those who had valid stage information. Because surgery is standard treatment for women with stage I–III breast cancer, we included only those who underwent breast surgery (either lumpectomy or mastectomy) between 6 months before to 12 months after cancer diagnosis (which is based on either biopsy or surgical pathology). Women who had a diagnosis of any previous cancer (excluding nonmelanoma skin cancer) and those residing in long-term care were excluded from the cohort. Cohort entry date was defined as the date of breast cancer diagnosis in the OCR. From the cohort of women with breast cancer, we identified those who were diagnosed with diabetes at least 180 days before cancer diagnosis through linkage to the ODD. Women with both diabetes and breast cancer were then matched for age (±1 year), cancer stage (I, II, or III), and year of diagnosis (calendar year) to two women with breast cancer but without diabetes. Control patients had no history of diabetes up to 1 year after breast cancer diagnosis.

Primary Exposure and Covariates

The primary exposure of interest was presence of diabetes, which was determined by linking to the ODD, a previously validated algorithm for identifying prevalent and incident diabetes. A diagnosis of diabetes is based on either two patient/physician claims for diabetes within a 2-year period or one hospitalization with a discharge diagnosis of diabetes (16).

Cardiovascular disease at baseline was defined as either myocardial infarction, stroke (including a transient ischemic event) (17) on the basis of a previously validated algorithm, or congestive heart failure, all by using OHIP billing claims and the CIHI Hospital Discharge Abstract Database and Same Day Surgery database. The look-back period for cardiovascular disease at baseline was 5 years.

The following baseline covariates were identified: age, quintile of median neighborhood income derived from census data on household income at the postal code level and rural residence (from RPDB), year of breast cancer diagnosis, stage of breast cancer (I, II, or III), comorbidity measured by using the weighted John Hopkins Aggregated Diagnosis Group (ADG) score (18,19) in the 2 years before the index cancer diagnosis date (for cancer cases), and comorbidities, including renal disease (chronic renal failure, renal dialysis) (20) and dementia, in the 5 years before the index diagnosis date. We were unable to account for BMI given the absence of clinical variables in the databases. In addition, we did not record medications because data are only available for individuals age ≥65 years in the databases.

Study Outcomes

We examined two sets of outcomes. First, we evaluated breast cancer treatment differences by comparing the proportion of women with and without diabetes who received chemotherapy and radiotherapy. Because these therapies are not indicated in all patients with breast cancer, we then defined guideline-adherent treatment as that recommended for subgroups of patients with breast cancer (21): *1*) chemotherapy for stage III disease and *2*) radiotherapy after lumpectomy. We recorded chemotherapy on the basis of chemotherapy-related codes in the OHIP and New Drug Funding Plan databases. To capture both neoadjuvant and adjuvant chemotherapy use, chemotherapy was identified up to 6 months before and 12 months after last surgery for breast cancer. We identified radiotherapy on the basis of radiotherapy-related codes in the OHIP and National Ambulatory Care Reporting System databases from the time of original breast surgery up to 12 months after the last breast surgery. Second, we compared all-cause and breast cancer–specific mortality between women with and without diabetes. We evaluated the effect of cancer treatments

received and comorbidities by adjusting for these variables. Death data were available from the vital statistics databases and the RPDB.

Data Analysis

Baseline characteristics and differences in proportions and means were compared between patients with breast cancer with and without diabetes.

Guideline-Adherent Breast Cancer Treatment Outcomes

For guideline-adherent treatment outcomes, we compared treatments between patients with and without diabetes by evaluating receipt of *1*) chemotherapy for women with stage III breast cancer and *2*) radiotherapy for women who underwent lumpectomy. We used two separate analyses. First, we compared the proportion of women with diabetes who received chemotherapy and radiotherapy in the follow-up period with that of women without diabetes to generate a relative risk (RR) ratio. Second, to be able to account for other covariates in the model, we created both unadjusted and adjusted cause-specific hazard models that accounted for the competing risk of death (22) to model the association between diabetes and the rate of exposure to chemotherapy and radiotherapy. The final multivariable model was selected on the basis of covariates that were predetermined to be clinically relevant and those that altered the hazard ratio (HR) estimate for diabetes by >10%. The covariates included in the final model were cardiovascular disease, chronic renal disease, dementia, and weighted ADG score. The models used a robust sandwich-type variance estimator to account for the matching.

All-Cause and Breast Cancer–Specific Mortality

To examine the association between diabetes and mortality, hazard regression models were used to compare the hazard of all-cause and breast cancer–specific mortality (23) between women with and without diabetes. To determine the impact of treatment modalities on mortality outcomes, we first fit a model that only adjusted for chemotherapy and radiotherapy, both modeled as time-dependent covariates. Our fully adjusted model also controlled for cardiovascular disease, chronic renal disease, dementia, and weighted ADG score as baseline covariates. We tested for interactions between diabetes and cardiovascular disease as well as between diabetes and treatments (chemotherapy and radiotherapy individually) for both all-cause and breast cancer–specific mortality. A robust variance estimator was used to account for the matched nature of the sample.

We performed a series of subgroup analyses to evaluate how diabetes affects both treatment and mortality outcomes. For all subgroup analyses, we rematched groups on age, stage, and year of cancer diagnosis when initial matched groups were broken. First, we stratified women by presence of cardiovascular disease at baseline because those with cardiovascular disease may be less likely to receive aggressive treatments for breast cancer. For this subgroup, women were also matched on the presence of cardiovascular disease (yes or no). Second, because older women with breast cancer may be less likely to receive aggressive treatments, we stratified women by age (<70 and ≥70 years) and repeated the analyses in both groups. Third, because women with a longer duration of diabetes may have more comorbidities, we dichotomized diabetes duration (<5 and ≥5 years) and repeated analyses within each stratum, comparing outcomes with women without diabetes. Analyses were conducted by using SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

We identified 4,955 women with breast cancer and diabetes and 9,910 matched control patients with breast cancer but without diabetes. Table 1 lists baseline characteristics overall and by diabetes status. Mean (SD) age at cancer diagnosis was 66.8 (11.3) years, with 44.5% of women <65 years of age at diagnosis. Women with diabetes had more outpatient primary care visits before breast cancer diagnosis; however, more women

Table 1—Baseline characteristics of women with breast cancer by baseline diabetes status

Characteristic	Total	Diabetes	No diabetes	*P* value
Patients, *n*	14,865	4,955	9,910	
Age at breast cancer diagnosis (years)	66.8 ± 11.3	66.8 ± 11.3	66.8 ± 11.3	—
Age-group (years), *n*				
<50	1,053	351	702	
50–59	2,727	909	1,818	
60–69	4,858	1,618	3,240	
70–79	4,084	1,363	2,721	
>80	2,143	714	1,429	
Cancer stage at diagnosis				—
I	6,339 (42.6)	2,113 (42.6)	4,226 (42.6)	
II	6,393 (43.0)	2,131 (43.0)	4,262 (43.0)	
III	2,133 (14.3)	711 (14.3)	1,422 (14.3)	
ADG score	12.0 ± 11	14.2 ± 11.4	10.8 ± 10.5	<0.001
Comorbidities				
Cardiovascular disease	822 (5.5)	352 (7.1)	470 (4.7)	<0.001
Stroke/TIA	262 (1.8)	150 (3.0)	112 (1.1)	<0.001
Acute MI/CHF	785 (5.3)	456 (9.2)	330 (3.3)	<0.001
Chronic renal disease	605 (4.1)	357 (7.2)	248 (2.5)	<0.001
Chronic dialysis	63 (0.4)	48 (1.0)	15 (0.2)	<0.001
Dementia	613 (4.1)	256 (5.2)	357 (3.6)	<0.001
Breast cancer surgery				
Mastectomy	5,534 (37.2)	1,911 (38.6)	3,623 (36.6)	0.015
Breast-conserving surgery	9,314 (62.8)	3,044 (61.4)	6,287 (63.4)	
Urban residence	12,860 (86.5)	4,352 (87.8)	8,508 (85.9)	<0.001
Income quintile				
1	2,823 (19.0)	1,118 (22.6)	1,705 (17.2)	0.015
2	2,960 (19.9)	1,059 (21.4)	1,901 (19.2)	—
3	2,836 (19.1)	952 (19.2)	1,884 (19.0)	
4	3,049 (20.5)	960 (19.4)	2,089 (21.1)	
5	3,139 (21.1)	845 (17.1)	2,294 (23.1)	

Data are mean ± SD or *n* (%) unless otherwise indicated. CHF, congestive heart failure; MI, myocardial infarction; TIA, transient ischemic attack.

without diabetes had an unplanned hospitalization in the year before cancer diagnosis (data not shown). Women with diabetes had significantly higher ADG scores than those without diabetes as well a higher prevalence of cardiovascular and renal comorbidities and dementia at baseline. A higher proportion of women with diabetes were in the lower income quintiles and lived in an urban setting.

Guideline-Adherent Cancer Treatment Outcomes

Table 2 shows the RRs and HRs for receipt of breast cancer treatments between women with and without diabetes. Among women with stage III breast cancer, in whom chemotherapy is considered guideline-adherent treatment, those with diabetes were slightly less likely to receive chemotherapy than those without diabetes (RR 0.93 [95% CI 0.89–0.97]). The results were similar in the overall cohort (chemotherapy RR 0.93 [0.89–0.96]) as well as in analyses stratified by the presence of cardiovascular disease, diabetes duration, and age >70 years. When adjusting for cardiovascular disease, renal disease, dementia, and weighted ADG score in the cause-specific hazard model (Table 2), no differences were found in the rate of receipt of guideline-adherent chemotherapy between groups (adjusted HR [aHR] 1.03 [95% CI 0.93–1.13]). Results were similar in all women with breast cancer (aHR 1.01 [0.97–1.06]) as well as in stratified analyses (Table 2).

For radiotherapy, women with diabetes treated with a lumpectomy were slightly less likely to receive radiotherapy than women with a lumpectomy without diabetes (RR 0.97 [95% CI 0.95–0.99]) as were women overall with diabetes (RR 0.93 [0.90–0.95]). In multivariable models in which we adjusted for cardiovascular disease, renal disease, dementia, and ADG score, no significant difference was found in the rate of receipt of radiotherapy between women with diabetes who had a lumpectomy and those without diabetes (aHR 0.98 [95% CI 0.94–1.02]), although overall, women with diabetes had modestly lower rates of radiotherapy compared with those without diabetes (aHR 0.94 [0.91–0.98]). The results remained unchanged on stratified analyses (Table 2).

Mortality

Results comparing mortality outcomes between women with breast cancer with

Table 2—RRs and HRs of receiving breast cancer treatments between women with and without diabetes

		Chemotherapy				Radiotherapy			
			HR unadjusted				HR unadjusted		
	*n**	RR (95% CI)	(95% CI)	*P* value	aHR† (95% CI)	*P* value	RR (95% CI)	(95% CI)	*P* value	aHR† (95% CI)	*P* value
Overall	4,955	0.93 (0.89–0.96)	0.89 (0.85–0.93)	<0.001	1.01 (0.97–1.06)	0.56	0.93 (0.90–0.95)	0.91 (0.87–0.94)	<0.001	0.94 (0.91–0.98)	0.003
Stage III	697	0.93 (0.89–0.97)	0.85 (0.77–0.93)	0.006	1.03 (0.93–1.13)	0.59	—	—	—	—	—
Lumpectomy only	2,708	—	—	—	—	—	0.97 (0.95–0.99)	0.96 (0.92–1.00)	0.03	0.98 (0.94–1.02)	0.32
CVD‡											
Yes	167	0.69 (0.43–1.09)	0.69 (0.43–1.09)	0.11	0.95 (0.79–1.15)	0.26	0.95 (0.79–1.15)	0.95 (0.73–1.23)	0.70	1.04 (0.80–1.35)	0.78
No	4,102	0.92 (0.88–0.97)	0.92 (0.88–0.97)	0.001	0.94 (0.91–0.97)	0.81	0.94 (0.91–0.97)	0.93 (0.89–0.97)	0.001	0.95 (0.91–0.99)	0.01
Age (years)											
<70	3,016	0.89 (0.85–0.94)	0.89 (0.85–0.94)	<0.001	0.95 (0.90–1.00)	0.06	0.92 (0.89–0.95)	0.91 (0.87–0.96)	<0.001	0.93 (0.89–0.97)	0.002
>70	1,896	0.82 (0.71–0.94)	0.82 (0.71–0.94)	0.04	0.91 (0.79–1.05)	0.19	0.93 (0.88–0.98)	0.90 (0.84–0.97)	0.005	0.95 (0.89–1.03)	0.21
Diabetes duration (years)											
<5	1,838	0.92 (0.86–0.99)	0.92 (0.86–0.99)	0.02	1.00 (0.93–1.07)	0.99	0.95 (0.91–0.99)	0.94 (0.89–1.00)	0.05	0.96 (0.90–1.02)	0.18
>5	3,117	0.89 (0.84–0.94)	0.82 (0.71–0.94)	<0.001	1.04 (0.97–1.10)	0.27	0.91 (0.88–0.94)	0.88 (0.84–0.93)	<0.001	0.92 (0.88–0.97)	0.002

CVD, cardiovascular disease (defined as cerebrovascular disease, acute myocardial infarction, and congestive heart failure). *2:1 matches. †Adjusted for CVD, chronic renal disease, dementia, and weighted ADG score. ‡Models in CVD (yes or no) subgroups adjusted for chronic renal disease, dementia, and weighted ADG score.

and without diabetes are presented in Table 3. In unadjusted models, women with diabetes had a significantly higher rate of all-cause and cancer-specific mortality (HR 1.42 [95% CI 1.30–1.55] vs. 1.24 [1.05–1.46], respectively). Adjusting for receipt of chemotherapy and radiotherapy alone did not alter these results (HR 1.40 [1.28–1.52] vs. 1.25 [1.06–1.48], respectively). The higher rate of all-cause mortality in women with diabetes was attenuated after further adjusting for cardiovascular disease, renal disease, dementia, and weighted ADG score (aHR 1.16 [95% CI 1.06–1.27]), although the association was no longer significant for breast cancer–specific mortality after adjustment (aHR 1.11 [0.94–1.31]). The interaction term between cardiovascular disease and diabetes on breast cancer–specific mortality was significant (P = 0.0069); however, no significant interaction was found between cardiovascular disease and diabetes on all-cause mortality or between diabetes and either chemotherapy or radiotherapy on all-cause or breast cancer–specific mortality.

In stratified analyses, the rate of all-cause mortality was similarly increased among all subgroups of women with breast cancer and diabetes, except for those with a duration of diabetes <5 years (aHR 1.02 [95% CI 0.86–1.21]). Breast cancer–specific mortality only remained increased among women with diabetes duration >5 years (aHR 1.25 [1.02–1.54]) and women with preexisting cardiovascular disease (aHR 2.19 [1.09–4.42]).

CONCLUSIONS

This large population-based study of women with breast cancer examined how the presence of diabetes affects cancer treatment patterns and prognosis. After accounting for cancer stage and other comorbidities, we showed that women with diabetes are as likely to receive guideline-adherent chemotherapy and radiotherapy as those without diabetes. Although we found that women with diabetes had a higher rate of all-cause mortality, breast cancer–specific mortality was increased only among women with a longer duration of diabetes and those with cardiovascular disease. The findings suggest that diabetes remains a risk factor for poorer breast cancer prognosis, particularly in women with long-standing

Table 3—Association between diabetes and all-cause mortality and breast cancer–specific mortality

	All-cause mortality						Breast cancer–specific mortality					
	HR (unadjusted) (95% CI)	P value	HR (treatments only*) (95% CI)	P value	HR (fully adjusted†) (95% CI)	P value	HR (unadjusted) (95% CI)	P value	HR (treatment only) (95% CI)	P value	HR (fully adjusted†) (95% CI)	P value
Overall	1.42 (1.30–1.55)	<0.001	1.40 (1.28–1.52)	0.01	1.16 (1.06–1.27)	0.001	1.24 (1.05–1.46)	0.01	1.25 (1.06–1.48)	0.008	1.11 (0.94–1.31)	0.23
CVD												
Yes	1.55 (1.16–2.07)	0.003	—	—	1.46 (1.09–1.97)‡	0.01	1.93 (1.01–3.69)	0.05			2.19 (1.09–4.42)‡	0.03
No	1.26 (1.13–1.41)	<0.001	—	—	1.14 (1.02–1.27)‡	0.03	1.06 (0.87–1.29)	0.54			0.99 (0.81–1.21)‡	0.90
Age (years)												
<70	1.46 (1.26–1.70)	<0.001	—	—	1.25 (1.07–1.46)	0.004	1.25 (0.99–1.58)	0.06			1.18 (0.92–1.50)	0.19
>70	1.43 (1.28–1.59)	<0.001	—	—	1.24 (1.10–1.38)	0.003	1.24 (0.98–1.57)	0.08			1.17 (0.92–1.49)	0.19
Diabetes duration (years)												
<5	1.17 (0.99–1.38)	0.06	—	—	1.02 (0.86–1.21)	0.80	0.99 (0.74–1.35)	0.97			0.93 (0.68–1.26)	0.62
>5	1.61 (1.45–1.79)	<0.001	—	—	1.28 (1.15–1.43)	<0.001	1.45 (1.18–1.77)	0.003			1.25 (1.02–1.54)	0.03

CVD, cardiovascular disease (defined as cerebrovascular disease, acute myocardial infarction, and congestive heart failure). *Adjusted for chemotherapy (time dependent) and radiotherapy (time dependent) only. †Adjusted for chemotherapy (time dependent), radiotherapy (time dependent), CVD, renal disease, dementia, and weighted ADG score. ‡Adjusted for chemotherapy (time dependent), radiotherapy (time dependent), renal disease, dementia, and weighted ADG score.

diabetes and those with established cardiovascular disease.

Similar to other studies, we found in unadjusted analyses that women with diabetes were modestly less likely to receive guideline-adherent breast cancer treatment than women without diabetes (5,12–14,24,25). However, these differences were eliminated when we adjusted for key confounders, such as the presence of cardiovascular disease. Previous studies did not specifically account for the presence of cardiovascular disease, only overall comorbidities, whereas some only evaluated the receipt of anthracycline, a cardiotoxic chemotherapy agent (5,24,25). Therefore, findings from these studies may reflect differences in baseline cardiovascular disease rather than the influence of diabetes per se. Another major difference between our studies and those published previously is that our study was conducted in a setting with universal access to cancer treatments. These findings are important because they show that after accounting for differences in comorbidities and access to care, women with diabetes and breast cancer receive appropriate cancer treatments as often as women without diabetes.

Despite comparable rates of treatment, women with diabetes had a 40% higher all-cause and 25% higher cancer-specific mortality rate compared with those without diabetes, similar to other studies (1,4,5,24). However, when we adjusted for comorbidities such as cardiovascular disease, renal disease, and dementia, the excess all-cause mortality associated with diabetes decreased to 16%, and the difference in breast cancer–specific mortality was no longer significant. These results suggest that the poorer breast cancer prognosis observed in women with diabetes is largely driven by diabetes-related comorbidities rather than by the diabetes itself. This hypothesis also is supported by the finding that higher cancer-specific mortality was only observed in women with longer-standing diabetes and with cardiovascular disease. To our knowledge, the current study provides novel information about key risk factors for poorer prognosis in women with breast cancer and diabetes after accounting for cancer stage and treatment benefits.

All-cause mortality after breast cancer remained higher among women with diabetes overall. As with cancer-specific mortality, this difference was greatest in women with a longer duration of diabetes and in those with cardiovascular disease. A reason for this finding may be that diabetes and cardiovascular disease are less aggressively managed in the setting of cancer treatments and surveillance, leading to higher noncancer mortality (26). Future studies to evaluate diabetes care patterns in patients with cancer may help to guide strategies to lessen this disparity in noncancer mortality.

Of note, we found that women with diabetes who had cardiovascular disease had a more than twofold increase in breast cancer–specific mortality compared with those without diabetes, whereas the effect of diabetes on all-cause mortality was more modest in this subgroup. Among women without cardiovascular disease, diabetes did not affect cancer-specific outcomes. One explanation for this finding is that women with diabetes may be more likely to experience chemotherapy-related toxicities (5,27), which may be further pronounced in those with cardiovascular disease. Higher toxicity rates may limit the dose and number of treatment courses received, thereby attenuating benefits on cancer outcomes. Alternatively, specific chemotherapy agents with higher cardiotoxicity, such as anthracyclines (28,29), may be offered less often to women with diabetes who have cardiovascular disease, resulting in less effective chemotherapy regimens. Other studies have found that women with diabetes are less likely to receive anthracycline chemotherapy (5). Additional studies are needed to better understand how the presence of cardiovascular disease affects cancer outcomes among patients with diabetes.

In this large population-based study, we evaluated the impact of diabetes on breast cancer treatments and outcomes. Strengths include population-based data in a universal health care setting, the availability of validated and comprehensive sources of diabetes and cancer diagnoses, and the ability to adjust for specific comorbidities and cancer stage. However, this study has some limitations. First, we used administrative databases and, thus, did not have access to metabolic markers of diabetes control (e.g., glycated hemoglobin), other risk factors, or cardiovascular imaging results (e.g., echocardiogram), which may have affected the study findings. For example we could not adjust for the possible impact of obesity in our analyses, which may have partly mediated the effects of diabetes on breast cancer prognosis (30,31). Furthermore, we did not include data on glucose-lowering medications because these would only have been available among women >65 years of age. However, in previous work, we did not find a significant impact of diabetes medications on breast cancer outcomes in older women with diabetes; therefore, we would not expect diabetes treatments to affect the results in this study (32). Second, we did not have comprehensive information on specific treatments, such as type of chemotherapy and use of anthracyclines, and we could not determine whether patients carried out the full treatment course or had more detailed information on cancer subtypes. Finally, although we did our best to account for measurable confounding variables, there is always a risk of unmeasured confounders that affect results in observational studies.

In summary, we have shown that after accounting for baseline differences in cancer stage and comorbidities, patients with breast cancer and diabetes are as likely to receive guideline-adherent chemotherapy and radiotherapy treatments and have comparable cancer-specific mortality as patients with breast cancer without diabetes. Higher breast cancer–specific mortality was seen only in women with longer diabetes duration and with coexisting cardiovascular disease. In contrast, all-cause mortality remained higher for women with diabetes even after accounting for these other risk factors. These findings provide important prognostic information to direct counseling and treatment of women with both diabetes and breast cancer. Additional studies to identify factors that contribute to noncancer-related mortality in this group will help to minimize the differences in outcomes between women with and without diabetes.

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