Impact of Baseline Cardiovascular Comorbidity on Outcomes in Women With Breast Cancer: A Real-world, Population-based Study

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Abstract

This is a retrospective, population-based study of patients with breast cancer. A total of 25,594 patients were included into this study. Patients with preexisting cardiovascular disease are less likely to received recommended anticancer treatment.

Introduction: The aim of this study was to characterize treatment trends and outcomes of women who have preexisting cardiovascular disease (CVD) prior to the diagnosis of breast cancer. **Patients and Methods:** This represented a retrospective, population-based cohort study that analyzed pooled data from the provincial cancer registry, physician billing claims, hospital discharge abstracts, ambulatory care, and the 2011 census in a large Canadian province. Multivariable logistic regression was performed to identify the associations of CVD with breast cancer treatment and outcomes. Kaplan-Meier analyses were conducted and survival was compared between CVD and non-CVD groups. Cox regression models were constructed to determine the effect of CVD on overall and cancer-specific survival. **Results:** A total of 25,594 women with breast cancer were eligible and included in the current analysis. Preexisting CVD was associated with a lower likelihood of receiving chemotherapy (odds ratio [OR], 0.56; 95% confidence interval [CI], 0.48-0.66; $P < .0001$) and radiotherapy (OR, 0.75; 95% CI, 0.67-0.83; $P < .0001$), but a higher probability of undergoing mastectomy (OR, 1.13; 95% CI, 1.03-1.25; $P = .011$). Unadjusted Kaplan-Meier analyses showed that individuals with preexisting CVD experienced worse median overall and cancer-specific survival when compared with those without CVD (87 vs. 150 months and 106 vs. 131 months, respectively; both $P < .0001$). Adjusting for measured confounders, the presence of preexisting CVD continued to predict for worse overall survival (hazard ratio, 1.55; 95% CI, 1.43-1.67; $P < .0001$), but not cancer-specific survival (hazard ratio, 1.11; 95% CI, 0.98-1.27; $P = .099$). **Conclusions:** Patients with breast cancer with preexisting CVD are less likely to receive recommended treatment for their cancer and more likely to exhibit worse overall survival.

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Introduction

Cancer and cardiovascular disease represent the 2 most common causes of mortality in developed countries. Because of this, an increasing number of patients with cancer have preexisting cardiovascular disease at the time of their malignant diagnosis, which can pose significant challenges to their oncologic care.[1] With the continued increase in life expectancy in the general population, the prevalence of comorbid cancer and cardiovascular disease is expected to rise.[2] The situation is particularly difficult in the context of breast cancer where common locoregional and

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systemic therapies carry significant risks of short- and long-term cardio-toxic effects.[3,4]

Adding further to this challenge is that the majority of prior cardio-oncology research has mainly emphasized the study of cardiac toxicities from anticancer therapies, but little is actually known about how the presence of one comorbidity affects the management of the other.[5] Because almost all randomized clinical trials exclude patients with a previous history of cardiovascular disorders from participation,[6,7] care of patients with breast cancer with preexisting cardiovascular disease represents a clinical scenario in which there is scarce evidence to guide optimal management.[8] As a result, there is likely high variability in the approach to care between physicians and between jurisdictions.

Given the concerns regarding safety, it is probable that oncology clinical trials will continue to limit enrollment of patients with cardiovascular disease. Thus, population-based studies of well-collected administrative data may represent the most ideal way of addressing questions related to this important clinical scenario. For this reason, the main objective of the current study is to provide a systematic evaluation of treatment trends and outcomes of women with preexisting cardiovascular comorbid conditions prior to their diagnosis of breast cancer. Our a priori hypothesis is that these women would be undertreated for their cancer and experience worse survival when compared with their counterparts who do not have baseline cardiovascular disease.

Patients and Methods

Data Sources and Study Population

This was a large, retrospective, population-based, cohort study that analyzed data from the Alberta cancer registry (ACR), provincial physician billing claims, hospital discharge abstracts, ambulatory care, vital statistics, and the 2011 census. The ACR covers the province's entire population, which is estimated to be about 4 million people during the study period. All patients have access to a single-payer, universal healthcare system. The ACR prospectively collects information on patient demographics, tumor characteristics, primary treatment, and oncology facility from all individuals with a confirmed cancer diagnosis and who resided in the province at the time of their initial diagnosis. The provincial physician billing claims data capture up to 3 International Classification of Diseases ninth version (ICD-9) coded diagnoses, 1 procedure code, physician specialty, and location of healthcare delivery. The hospital discharge abstracts include information about all inpatient encounters (by hospital discharge or death) across the province. Up to 25 ICD-10-coded diagnoses and up to 20 Canadian Classification of Health Interventions-coded procedures are recorded in each discharge abstract. The ambulatory care data further consist of up to 10 ICD-10 recorded diagnoses and 10 Canadian Classification of Health Interventions-coded procedures. These datasets were linked deterministically by a unique lifetime patient provincial health number.

Women aged 18 years and older with a diagnosis of breast cancer between January 1, 2004 and December 31, 2015 in Alberta, Canada were included. Patients without an Alberta healthcare number, those who moved out of province within 1 year of primary treatment, those who had more than 1 type of primary tumor, or those with unknown status of cardiovascular disease were excluded. This study was approved by the Health Research Ethics Board of Alberta's Cancer Committee (HREBA.CC-17-0183).

Definition of Variables

Outcomes. Information on all-cause deaths and cancer-specific deaths were obtained from vital statistics. Primary surgery type was defined as the latest definitive surgical procedure (if multiple) performed within 1 year of diagnosis. For example, this meant that a patient who had undergone breast conserving surgery (BCS) first, but who received a mastectomy 1 year later would be categorized as having a mastectomy. Using physician billing claims data, mastectomy was identified as at least 1 surgeon claim coded as mastectomy. Patients who underwent surgery but not a mastectomy were considered as having a BCS. Information on the receipt of adjuvant treatment including radiation therapy, hormonal therapy, and chemotherapy were recorded in the ACR. For this study, these data elements were dichotomized in a binary fashion (yes/no).

Independent Variables. Using a combination of data from the ACR, discharge abstracts, ambulatory care and physician billing claims, the presence of cardiovascular disease, including myocardial infarction, congestive heart failure, arrhythmias, and cerebrovascular disease, at or preceding the time of the cancer diagnosis were identified using well-established and previously validated ICD algorithms.[9] American Joint Committee on Cancer stage, tumor grade, histologic type, molecular subtype (based on estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status), treating institution type (academic/community) and postal code were obtained from the ACR. The Charlson comorbidity score was generated from the discharge abstracts, ambulatory care data, and physician billing claims data.[9] Using the patients' postal code at diagnosis, neighborhood socioeconomic status including education and income levels were derived based on the 2011 census. Postal codes were also used to calculate driving time to the nearest cancer center using Google Maps API. Driving time was categorized as $\leq$ 60, 61-120, and $>$ 120 minutes as per previously published literature.[10] The province is divided strategically into health regions as an approach to better define catchment areas, deliver care, and assess outcomes at the population level.[11] Each patient was assigned to one of the health regions based on their postal code at diagnosis.

Statistical Analysis

Descriptive analyses were conducted to summarize patient, tumor, and system characteristics. The Student t test and Wilcoxon rank-sum test were used to compare continuous variables, whereas the χ^2 and Fisher exact tests were applied to compare categorical variables, when applicable. Multivariable logistic regression models were constructed to identify associations between preexisting cardiovascular disease and cancer treatment patterns. Unadjusted and adjusted Kaplan-Meier curves were plotted to describe survival differences between groups with and without cardiovascular disease, and compared with the log rank test. Cox proportional hazards models were developed to study the effect of preexisting cardiovascular disease on overall survival and cancer-specific survival. Overall survival was defined as the

Table 1 Characteristics of the Cohort

Parameter	All Patients (N = 25,594), n (%)	Patients Without CVD (N = 23,041), n (%)	Patients With Preexisting History of CVD (N = 2553), n (%)	*P* Value
Mean age, y (SD)	59.18 (13.42)	60.43 (13.85)	71.71 (12.59)	< .0001
Charlson comorbidity index				< .0001
0	15,933 (69.2)	16,854 (65.9)	921 (36.1)	
1	3934 (17.1)	4553 (17.8)	619 (24.2)	
≥ 2	3174 (13.8)	4187 (16.4)	1013 (39.7)	
Overall stage				< .0001
0	2961 (12.9)	3154 (12.3)	193 (7.6)	
I	8791 (38.2)	9776 (38.2)	985 (38.6)	
II	7300 (31.7)	8198 (32)	898 (35.2)	
III	2618 (11.4)	2938 (11.5)	320 (12.5)	
IV	1075 (4.7)	1169 (4.6)	94 (3.7)	
Unknown	296 (1.3)	359 (1.4)	63 (2.5)	
T stage				< .0001
T0	3035 (13.2)	3232 (12.6)	197 (7.7)	
T1	11,169 (48.5)	12,367 (48.3)	1198 (46.9)	
T2	6450 (28)	7323 (28.6)	873 (34.2)	
T3	1138 (4.9)	1275 (5)	137 (5.4)	
T4	989 (4.3)	1099 (4.3)	110 (4.3)	
Unknown	260 (1.1)	298 (1.2)	38 (1.5)	
N stage				< .0001
N0	15,387 (66.8)	17,068 (66.7)	1681 (65.8)	
N1	5060 (22)	5579 (21.8)	519 (20.3)	
N2	1310 (5.7)	1448 (5.7)	138 (5.4)	
N3	857 (3.7)	966 (3.8)	109 (4.3)	
Unknown	427 (1.9)	533 (2.1)	106 (4.2)	
Histology				< .0001
Ductal	16,651 (72.3)	18,534 (72.4)	1883 (73.8)	
Lobular	1602 (7)	1853 (7.2)	251 (9.8)	
Others	4788 (20.8)	5207 (20.3)	419 (16.4)	
Subtype				< .0001
$HER2^+$	1627 (7.1)	1779 (7)	152 (6)	
$HER2^-$, ER^+/PR^+	16,913 (73.4)	18,901 (73.8)	1988 (77.9)	
Triple negative	2629 (11.4)	2891 (11.3)	262 (10.3)	
Unknown	1872 (8.1)	2023 (7.9)	151 (5.9)	
Institution				.8007
Academic	13,279 (57.6)	14,757 (57.7)	1478 (57.9)	
Community	9762 (42.4)	10,837 (42.3)	1075 (42.1)	
Year of diagnosis				.017
2004-2009	10,217 (44.3)	11,286 (44.1)	1069 (41.9)	
2010-2015	12,824 (55.7)	14,308 (55.9)	1484 (58.1)	
Grade				< .0001
Low	3893 (16.9)	4383 (17.1)	490 (19.2)	
Moderate	8591 (37.3)	9682 (37.8)	1091 (42.7)	
High	8017 (34.8)	8818 (34.5)	801 (31.4)	
Unknown	2540 (11)	2711 (10.6)	171 (6.7)	
Laterality				.403
Bilateral	14 (0.1)	0 (0)	14 (0.1)	
Right	12,906 (50.4)	1316 (51.5)	11,590 (50.3)	

Table 1 Continued

Parameter	All Patients (N = 25,594), n (%)	Patients Without CVD (N = 23,041), n (%)	Patients With Preexisting History of CVD (N = 2553), n (%)	*P* Value
Left	12,352 (48.3)	1205 (47.2)	11,147 (48.4)	
Unknown	322 (1.3)	32 (1.3)	290 (1.3)	
Surgery				< .0001
BCS	9732 (42.2)	10,771 (42.1)	1039 (40.7)	
Mastectomy	10,260 (44.5)	11,595 (45.3)	1335 (52.3)	
Not done	3049 (13.2)	3228 (12.6)	179 (7)	
Radiotherapy				< .0001
Yes	12,488 (54.2)	13,474 (52.6)	986 (38.6)	
No	10,553 (45.8)	12,120 (47.4)	1567 (61.4)	
Chemotherapy				< .0001
Yes	8959 (38.9)	9420 (36.8)	461 (18.1)	
No	14,082 (61.1)	16,174 (63.2)	2092 (81.9)	
Death from cancer				.001
No	20,682 (89.8)	22,922 (89.6)	2240 (87.7)	
Yes	2359 (10.2)	2672 (10.4)	313 (12.3)	
Driving time to nearest cancer center, h				< .0001
1	18,397 (79.8)	20,356 (79.5)	1959 (76.7)	
2	2566 (11.1)	2930 (11.4)	364 (14.3)	
3	2078 (9)	2308 (9)	230 (9)	
Education level				< .0001
≤ 80%	8436 (36.6)	9502 (37.1)	1066 (41.8)	
> 80%[a]	11,614 (50.4)	12,821 (50.1)	1207 (47.3)	
Unknown	2991 (13)	3271 (12.8)	280 (11)	
Income level, $				< .0001
≤ 46k	10,623 (46.1)	11,976 (46.8)	1353 (53)	
> 46k	9045 (39.3)	9904 (38.7)	859 (33.6)	
Unknown	3373 (14.6)	3714 (14.5)	341 (13.4)	
Health region				< .0001
Calgary	8613 (37.4)	9480 (37)	867 (34)	
Central	2909 (12.6)	3292 (12.9)	383 (15)	
Edmonton	7601 (33)	8435 (33)	834 (32.7)	
North	2106 (9.1)	2317 (9.1)	211 (8.3)	
South	1812 (7.9)	2070 (8.1)	258 (10.1)	

Abbreviation: BCS = Breast conserving surgery; CVD = cardiovascular disease including: myocardial infarction, cerebrovascular disease, or congestive heart failure; ER^+ = estrogen receptor-positive; HER^+ = human epidermal growth factor receptor 2-positive; HER^- = human epidermal growth factor receptor 2-negative; PR^+ = progesterone receptor-positive.
[a]80% of residents have high school and above level of education in the neighborhood.

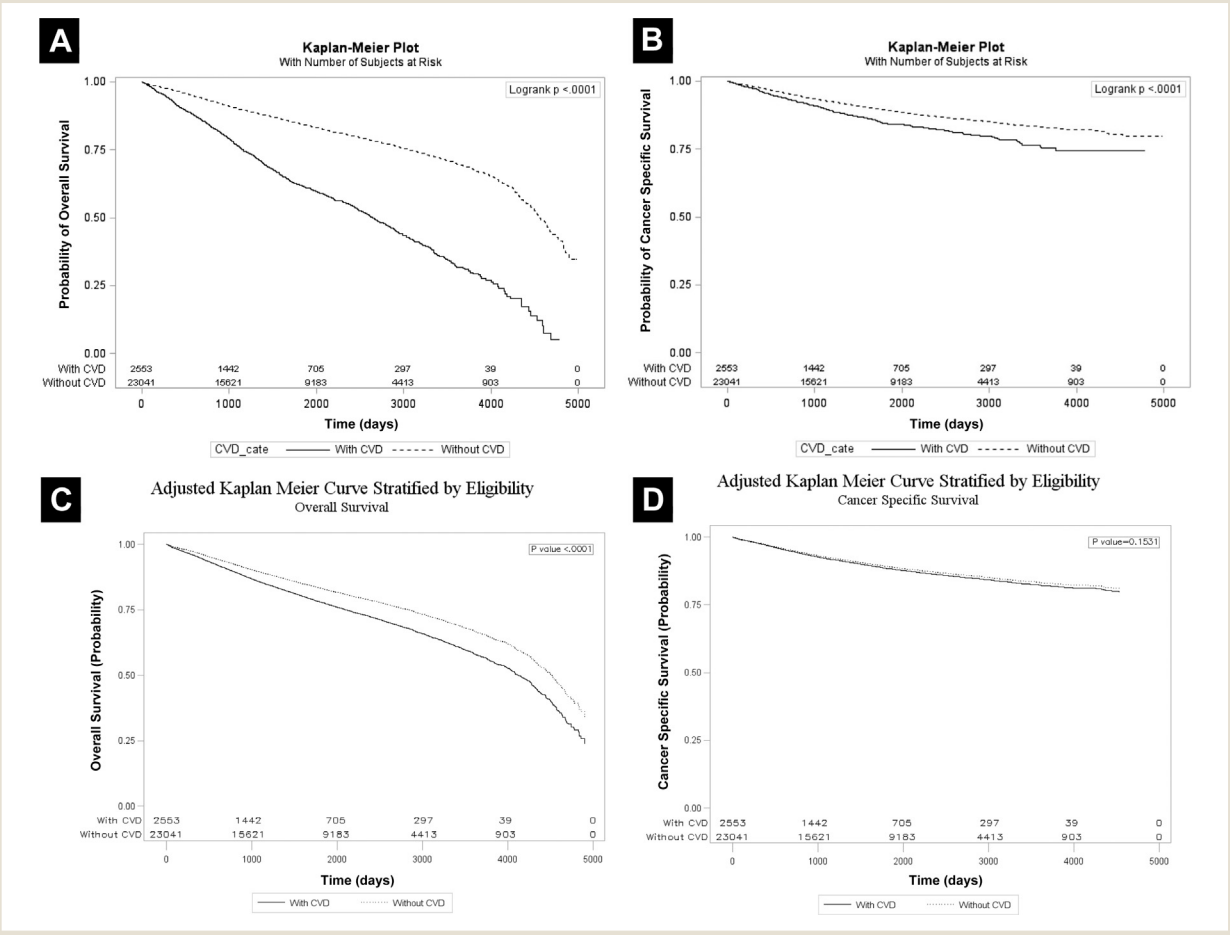
time interval between the date of cancer diagnosis and date of death from any cause, whereas cancer-specific survival was defined as the time interval between the date of cancer diagnosis and the date of death from cancer. Subgroup analyses were performed to investigate whether the effects of cardiovascular disease on outcomes were modified by age, stage, and different treatments. These analyses also assessed the interaction between cardiovascular disease and other independent variables in the multivariable model. All analyses were performed with SAS statistical software version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Patient Characteristics

A total of 25,594 women with breast cancer were eligible and included in the current analysis. Among them, 2553 (8%) patients had preexisting comorbid cardiovascular disease of whom 276 (1.1%) had myocardial infarction, 460 (1.8%) had congestive heart failure, 500 (2.0%) had cardiac arrhythmia, 673 (2.6%) had cerebrovascular disease, and 644 (2.5%) had more than 1 cardiovascular condition. In comparison, patients with baseline cardiovascular disease were more likely to be older ($P < .0001$), have a higher comorbidity burden

Figure 1 Kaplan-Meier Curve for the Impact of Preexisting Cardiovascular Disease. A, Unadjusted for Overall Survival; B, Unadjusted for Cancer-specific Survival; C, Adjusted for Overall Survival; and D, Adjusted for Cancer-specific Survival



Abbreviation: CVD = cardiovascular disease.

($P < .0001$), more advanced stage ($P < .0001$), lower grade disease ($P < .0001$), lobular histology ($P < .0001$), and luminal breast cancer ($P < .0001$) than those without prior cardiovascular disease. Moreover, they were more likely to be treated with mastectomy instead of BCS ($P < .0001$), but they were less likely to receive chemotherapy ($P < .0001$) or undergo radiotherapy ($P < .0001$). In addition, patients with a history of cardiovascular morbidity appeared to reside further away from urban areas ($P < .0001$) and cancer centers ($P < .0001$), and also reported lower educational ($P < .0001$) and income ($P < .0001$) levels. Additional details regarding these associations are described in Table 1.

Impact of Cardiovascular Disease on Breast Cancer Treatment

Using multivariate logistic regression analysis, the impact of cardiovascular disease on therapeutic decisions for breast cancer was assessed. Adjusting for age, Charlson comorbidity score, education, income, breast tumor subtype, histology, grade, stage, and year of diagnosis, treating facility, driving time to nearest cancer center and health region, preexisting cardiovascular disease was associated with a lower likelihood of receiving chemotherapy (odds ratio [OR], 0.56; 95% confidence interval [CI], 0.48-0.66; $P < .0001$) and radiotherapy (OR, 0.75; 95% CI, 0.67-0.83; $P < .0001$) but a higher probability of undergoing mastectomy (OR, 1.13; 95% CI, 1.03-1.25; $P = .011$).

Association of Cardiovascular Disease with Outcomes

Using unadjusted Kaplan-Meier analyses and log-rank tests, overall and cancer-specific survivals were evaluated based on the presence of preexisting cardiovascular morbidity. For both survival endpoints, baseline cardiovascular disease was associated with worse outcomes ($P < .0001$ for both overall and cancer-specific survival) (Figure 1A, B). Conversely, after controlling for confounders such as age, Charlson comorbidity score, education, income, breast tumor subtype, stage and year of diagnosis, histology, grade, chemotherapy, radiotherapy, surgery, treating institution, driving time to nearest cancer center, and health region, preceding cardiovascular disease was correlated with only worse overall survival ($P < .0001$), but not cancer-specific survival ($P = .1531$) (Figure 1C, D).

Table 2 Multivariate Cox Regression Analysis for Factors Associated With Overall Survival

Parameters	HR (95% CI)	*P* Value
CVD		
No	Reference	
Yes	1.545 (1.430-1.669)	< .0001
Charlson comorbidity index[a]		
0	Reference	
1	1.304 (1.196-1.422)	< .0001
≥ 2	1.678 (1.545-1.822)	< .0001
Treating institution		
Academic	Reference	
Community	1.071 (0.998-1.150)	.058
Driving time to nearest cancer center, h		
1	Reference	
2	1.01 (0.911-1.12)	.851
3	0.94 (0.799-1.107)	.461
Zone		
Calgary	Reference	
Central	1.05 (0.946-1.165)	.357
Edmonton	1.161 (1.081-1.246)	< .0001
North	1.245 (1.047-1.48)	.013
South	1.176 (1.041-1.327)	.0089
Age category, y		
≤ 40	Reference	
41-50	0.826 (0.703-0.971)	.020
51-60	1.088 (0.933-1.27)	.281
61-70	1.37 (1.173-1.6)	< .0001
71-80	2.426 (2.071-2.841)	< .0001
> 80	4.511 (3.834-5.308)	< .0001
Laterality		
Left	Reference	
Right	1.023 (0.966-1.082)	.439
Chemotherapy		
No	Reference	
Yes	0.785 (0.719-0.857)	< .0001
Radiotherapy		
No	Reference	
Yes	0.605 (0.56-0.655)	< .0001
Stage		
0	Reference	
I	3.051 (2.517-3.697)	< .0001
II	5.367 (4.432-6.501)	< .0001
III	14.284 (11.716-17.415)	< .0001
IV	31.142 (25.571-37.927)	< .0001
Subtype		
$HER2^+$	Reference	
$HER2^-$, ER^+/PR^+	1.157 (1.002-1.337)	.047
Triple negative	1.833 (1.57-2.138)	< .0001
Histology		
Ductal	Reference	
Lobular	1.011 (0.911-1.122)	.839
Others	1.101 (1.004-1.207)	.04
Grade		
Low	Reference	
Moderate	1.234 (1.122-1.358)	< .0001
High	1.848 (1.668-2.047)	< .0001
Surgery		
BCS	Reference	
Mastectomy	0.96 (0.885-1.041)	.323
Not done	2.451 (2.197-2.735)	< .0001
Education level		
≤ 80%	Reference	
> 80%[b]	0.989 (0.922-1.061)	.762
Income level, $		
≤ 46k	Reference	
> 46k	0.908 (0.846-0.975)	.007
Year (continuous)	1.04 (1.028-1.052)	< .0001

Abbreviation: BCS = breast conserving surgery; CI = confidence interval; CVD = cardiovascular disease including: myocardial infarction, cerebrovascular disease, or congestive heart failure; ER^+ = estrogen receptor-positive; HER^+ = human epidermal growth factor receptor 2-positive; HER^- = human epidermal growth factor receptor 2-negative; HR = hazard ratio; PR^+ = progesterone receptor-positive.

[a]Charlson comorbidity index calculations did not include age, cancer diagnosis/stage, or CVD comorbidity to avoid duplication in the model.

[b]80% of residents have high school and above level of education in the neighborhood.

Multivariate Cox regression analysis was conducted to determine all measured factors affecting outcomes. Advanced age, worse comorbidity, lower income, higher stage or grade, triple-negative disease, and lack of chemotherapy, radiation, or surgery were independently predictive of worse overall and cancer-specific survival (all $P < .05$). Of note, cardiovascular disease was also correlated with inferior overall survival (hazard ratio [HR], 1.55; 95% CI, 1.43-1.67; $P < .0001$), but not cancer-specific survival (HR, 1.11; 95% CI, 0.98-1.27; $P = .099$) in the models. Because the presence of cardiovascular disease may modify the impact of treatment on outcomes, we examined for effect modification by considering an interaction term in our models. For overall survival, the effect of cardiovascular morbidity on overall survival varied for chemotherapy ($P = .005$) and surgery ($P < .0001$), but not for radiotherapy ($P = .650$). For cancer-specific survival, none of the interactions were significant (P for chemotherapy, surgery, and radiotherapy were .614, .250, and .870, respectively). Finally, we characterized the effect of each cardiovascular disease separately on cancer-specific outcomes. The presence of myocardial infarction (HR, 0.91; 95% CI, 0.61-1.37; $P = .654$), congestive heart failure (HR, 1.26; 95% CI, 0.96-1.75; $P = .167$), arrhythmia (HR, 0.93; 95% CI, 0.73-1.17; $P = .522$), and cerebrovascular disease (HR, 1.12; 95% CI, 0.87-1.44; $P = .386$) did not predict for worse cancer-specific survival, even after adjusting for differences in treatment. However, a history of multiple

Table 3 Multivariate Cox Regression Analysis for Factors Associated With Cancer-specific Survival

Parameters	HR (95% CI)	*P* Value
CVD		
No	Reference	
Yes	1.114 (0.98-1.266)	.099
Charlson comorbidity index[a]		
0	Reference	
1	1.114 (0.985-1.261)	.086
≥ 2	1.258 (1.116-1.42)	.0002
Treating institution		
Academic	Reference	
Community	1.036 (0.938-1.145)	.482
Driving time to nearest cancer center, h		
1	Reference	
2	1.03 (0.894-1.188)	.680
3	0.922 (0.738-1.152)	.474
Health region		
Calgary	Reference	
Central	1.095 (0.951-1.261)	.207
Edmonton	1.151 (1.045-1.269)	.004
North	1.355 (1.074-1.709)	.010
South	1.236 (1.045-1.462)	.013
Age category, y		
≤ 40	Reference	
41-50	0.856 (0.719-1.02)	.082
51-60	0.981 (0.828-1.161)	.819
61-70	1.088 (0.914-1.296)	.340
71-80	1.388 (1.153-1.669)	.005
> 80	1.854 (1.525-2.255)	< .0001
Chemotherapy		
No	Reference	
Yes	0.731 (0.655-0.816)	< .0001
Radiotherapy		
No	Reference	
Yes	0.715 (0.642-0.797)	< .0001
Overall stage		
0	Reference	
I	19.98 (10.758-37.11)	< .0001
II	59.687 (32.323-110.216)	< .0001
III	206.124 (111.407-381.371)	< .0001
IV	582.09 (315.218-1074.904)	< .0001
Subtype		
$HER2^+$	Reference	
$HER2^-$, ER^+/PR^+	1.16 (0.972-1.385)	.1002
Triple negative	2.265 (1.878-2.731)	< .0001
Laterality		
Left	Reference	
Right	1.024 (0.948-1.106)	.549
Histology		
Ductal	Reference	
Lobular	1.086 (0.94-1.256)	.263
Others	1.095 (0.966-1.241)	.155
Grade		
Low	Reference	
Moderate	1.851 (1.548-2.212)	< .0001
High	3.401 (2.838-4.077)	< .0001
Surgery		
BCS	Reference	
Mastectomy	1.219 (1.084-1.372)	.001
Not done	2.829 (2.423-3.303)	< .0001
Education level		
≤ 80%	Reference	
> 80%[b]	1.036 (0.942-1.139)	.463
Income level, $		
≤ 46k	Reference	
> 46k	0.864 (0.785-0.951)	.002
Year (continuous)	0.983 (0.969-0.997)	.018

Abbreviation: BCS = breast conserving surgery; CI = confidence interval; CVD = cardiovascular disease including: myocardial infarction, cerebrovascular disease, or congestive heart failure; ER^+ = estrogen receptor-positive; HER^+ = human epidermal growth factor receptor 2-positive; HER^- = human epidermal growth factor receptor 2-negative; HR = hazard ratio; PR^+ = progesterone receptor-positive.
[a]Charlson comorbidity index calculations did not include age, cancer diagnosis/stage, or CVD comorbidity to avoid duplication in the model.
[b]80% of residents have high school and above level of education in the neighborhood.

cardiovascular diseases showed an association with worse outcomes (HR, 1.31; 95% CI, 1.03-1.66; $P = .029$). In addition, causes of death among patients with breast cancer with a cardiac history who died but who did not receive adjuvant treatment consisted of cardiovascular disease in 32.0%, breast cancer in 27.3%, and other causes in 40.7% of cases (Tables 2 and 3).

Discussion

The current study provides a real-life, population-based evaluation of the impact of preexisting cardiovascular disease on therapeutic decisions and outcomes among women with breast cancer. This adds to the literature because the majority of prior research in cardio-oncology has focused on characterizing the cardiac effects of oncology interventions, such as systemic therapy or radiation, whereas relatively little has been done to better describe how the presence of one comorbidity affects the management and outcome of the other. Our results showed that healthcare providers tended to undertreat the subset of patients with premorbid cardiovascular disease, particularly in terms of locoregional and systemic anticancer therapies for breast cancer. In turn, these patients experienced worse overall survival. In the absence of a similar impact on cancer-specific survival, worse outcomes in those with cardiovascular disease are likely attributed to excess noncancer related deaths.

In addition, our analysis demonstrated that sociodemographic factors correlated with breast cancer outcomes. For example, patients with higher income levels appeared to experience better overall and cancer-specific survival, which is largely consistent with prior studies conducted in Canada and other countries.[12] Nonetheless, the reasons for this association remain uncertain because Canada's single payer model is designed and structured such that almost all patients are able to access similar healthcare regardless of income. One hypothesis is that geography may be a barrier to healthcare access whereby those with lower incomes may tend to reside in rural areas that are further away from cancer centers. Conversely in the United States, income can impact insurance coverage, which may increase the risk of patients with lower socioeconomic status to present with more advanced stage at diagnosis and who may subsequently be less fit to receive appropriate standard therapy.[13,14]

Unadjusted Kaplan-Meier analysis showed that patients with preexisting cardiovascular morbidity tended to experience worse cancer-specific survival. This is likely because these patients were less likely to receive radiation and chemotherapy when compared with their counterparts without premorbid cardiovascular disease. Importantly, upon accounting for this treatment disparity in the adjusted Kaplan-Meier analysis and in the multivariate Cox regression models, this association was no longer evident. This suggests that undertreatment may be clinically appropriate in some patients. Our exploratory analysis showed that a significant proportion of untreated patients with breast cancer with a cardiac history actually died of either heart disease or other noncancer causes, highlighting that undertreatment of cancer likely did not contribute to their deaths in these cases. However, the lack of a significant interaction between cardiovascular disease and treatment on cancer-specific survival also indicates that carefully selected patients with cardiovascular morbidity are as likely as patients without cardiovascular disease to derive a similar outcome benefit from breast cancer treatments. This finding is clinically important and underscores to clinicians that breast cancer treatments should not be uniformly withheld from patients on the basis of cardiovascular disease alone. Careful consideration of symptoms and severity are likely important in the treatment decision-making process with patients. Indeed, our analysis found that the presence of multiple cardiovascular diseases, which is a reasonable clinical indicator of severity, was uniquely associated with poorer survival.

There are several limitations to this study. First, some important prognostic information was missing from the databases, including performance status. Such data elements are consistently unavailable from administrative data, and we tried to minimize the effect of this by considering the Charlson comorbidity index in our analyses. Another limitation is that we used claims-based definitions of cardiovascular disease, thus we cannot ensure that all clinically relevant cases were captured. Nonetheless, use of claims data to identify specific comorbidities is increasingly frequent and has been previously validated.[15] Importantly, these limitations should be balanced against the study's strengths, including its relatively large number of patients, the context of a single payer healthcare system that removes selection bias secondary to lack of insurance coverage, and the comprehensiveness of data that was provided by linking multiple administrative data sources. The latter permitted us to capture a sufficient number of rare events, such as cardiovascular disease, as well as ascertain an assessment of a patient's cancer and noncancer medical history and management over time and at several time points.

In conclusion, patients with breast cancer with preexisting cardiovascular disease are less likely to receive specific treatments for their breast cancer, such as radiation and chemotherapy, and they are more likely to experience worse overall survival. Our data suggest that some of these patients, when carefully selected, may still derive a similar magnitude of benefit from cancer treatments. However, the retrospective nature of our study design should caution against strong conclusions regarding the broad and unselected use of adjuvant treatment in this cohort of patients. Rather, considering the aging population and the anticipated increase in incidence of both cancer and cardiovascular disease, developing a formal and well-articulated plan that enables and facilitates improved comanagement of these 2 comorbidities should be a key priority of healthcare systems.

Clinical Practice Points

- This is a retrospective, population-based cohort study that analyzed pooled data from the provincial cancer registry, physician billing claims, hospital discharge abstracts, ambulatory care, and the 2011 census in a large Canadian province.
- Multivariable logistic regression was performed to identify the associations of CVD with breast cancer treatment and outcomes. Kaplan-Meier analyses were conducted, and survival was compared between CVD and non-CVD groups.
- A total of 25,594 women with breast cancer were eligible and included in the current analysis.
- Preexisting CVD was associated with a lower likelihood of receiving chemotherapy (OR, 0.56; 95% CI, 0.48-0.66; $P < .0001$) and radiotherapy (OR, 0.75; 95% CI, 0.67-0.83; $P < .0001$), but a higher probability of undergoing mastectomy (OR, 1.13; 95% CI, 1.03-1.25; $P = .011$).
- Unadjusted Kaplan-Meier analyses showed that individuals with preexisting CVD experienced worse median overall and cancer-specific survival when compared with those without CVD (87 vs. 150 months and 106 vs. 131 months, respectively; both $P < .0001$).
- Adjusting for measured confounders, the presence of preexisting CVD continued to predict for worse overall survival (HR, 1.55; 95% CI, 1.43-1.67; $P < .0001$), but not cancer-specific survival (HR, 1.11; 95% CI, 0.98-1.27; $P = .099$).
- Patients with breast cancer with preexisting CVD are less likely to receive recommended treatment for their cancer and more likely to exhibit worse overall survival.

Disclosure

The authors have stated that they have no conflicts of interest.

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