Original Article

Cardiovascular disease risk in long-term breast cancer survivors: A population-based cohort study

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BACKGROUND: Breast cancer survival is increasing, making late effects such as cardiovascular disease (CVD) more relevant. The purpose of this study was to evaluate incident CVD following breast cancer diagnosis among long-term survivors and to investigate possible risk factors for CVD. **METHODS:** A population-based cohort of 6641 breast cancer survivors diagnosed between 1997 and 2009 who survived at least 10 years was identified within the Utah Cancer Registry. In addition, 36,612 cancer-free women from the general population, matched by birth year and state, were identified within the Utah Population Database. Cox proportional hazards models were used to calculate CVD hazard ratios (HRs) for >10 to 15 and >15 years. **RESULTS:** Long-term breast cancer survivors had an increased risk of newly diagnosed diseases of the circulatory system (HR, 1.32; 99% confidence interval [CI], 1.00-1.75) from 10 to 15 years following cancer diagnosis compared with the general population. No increased CVD risks were observed after 15 years. Breast cancer survivors with Charlson Comorbidity Index score ≥2 had a significantly higher risk of diseases of the circulatory system (HR, 2.64; 95% CI, 1.08-6.45) beyond 10 years following breast cancer diagnosis. Similarly, older age, obesity, lower education, and family history of CVD and breast cancer were risk factors for heart and circulatory system diseases among long-term breast cancer survivors. **CONCLUSION:** Risk of CVD compared to the general population was moderate among this cohort of long-term breast cancer survivors between 10 to 15 years since cancer diagnosis. Awareness of CVD risks is important for breast cancer survivors. ***Cancer* 2022;128:2826-2835**. © *2022 American Cancer Society*.

KEYWORDS: breast cancer, cancer survivorship, cardiovascular diseases, late effects, matched cohort study.

INTRODUCTION

The number of breast cancer survivors in the United States (US) is expected to surpass 4 million by 2026.[1] Nearly 3.8 million breast cancer survivors in the United States were alive in 2020, with an additional 276,480 new cases diagnosed that year.[1] The continued improvement in survival for breast cancer is due, in part, to breast cancer treatment effectiveness and early screening practices and detection.[2] Hence the 5-year survival rate of breast cancer was 90%, based on 2010-2016 data.[3] With the long-term survival following breast cancer diagnosis, late effects of treatment such as cardiovascular disease (CVD) are a concern.

Previous population-based studies of CVD risks between 4 and 10 years following a breast cancer diagnosis in breast cancer survivors compared to general population cohorts reported inconsistent findings.[4-9] One questionnaire-based study that reported CVD outcomes >10 years after breast cancer diagnosis did not find an increased heart disease risk among breast cancer survivors compared with cancer-free women from the general population; there were few CVD events >15 years after cancer diagnosis to estimate risks.[8]

Among current risk factor studies for cardiovascular outcomes among breast cancer survivors, nearly all were based on a follow-up time of <10 years, were limited to older women over 65 years of age and Medicare recipients[10-18] or those diagnosed before 2002,[11,19] and none had cancer-free comparisons. The purpose of our study is to evaluate incident cardiovascular diseases following breast cancer diagnosis among a contemporary cohort of long-term breast cancer survivors compared to a general population cohort of women without cancer and to investigate possible risk factors for late onset CVDs among breast cancer survivors.

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MATERIALS AND METHODS

Study Population

Women diagnosed with a first primary breast cancer (primary site ICD-O-3 C50.0 to C50.9) identified within the Utah Cancer Registry (UCR) were included in the study. For eligibility, women had to be 1) Utah residents, 2) ≥18 years of age at the time of diagnosis, and 3) diagnosed between 1997 and 2017 with breast cancer. Breast cancer survivors were matched on birth year (±2 years) and birth state with up to 5 cancer-free women from the general population. Eligibility criteria for the general population were that women had lived in Utah since 1996 or were ≤30 years of age at the time they first moved to Utah to assure adequate follow-up time for the women from the general population to become a case. A total of 783 breast cancer survivors were excluded for unknown stage (Fig. 1). We also restricted the study population to women with >10 years of follow-up (that also meant that the last diagnosis year started in 2009), and the final sample size was 6641 breast cancer survivors and 36,612 women in the general population cohort.

Data Sources and Outcome Measures

The Utah Population Database (UPDB) contained records from the UCR, Utah driver's license, statewide vital, demographic, and family history information that link to medical information. All cancer patients from the Utah Cancer Registry are linked to the UPDB. UPDB uses record linking IBM InfoSphere QualityStage software to perform probabilistic records linking to various databases, including the UCR. Variables from the UCR included: age at cancer diagnosis (years), birth year, race, ethnicity, rural residence, treatment (surgery, chemotherapy, radiotherapy, and endocrine therapy), tumor grade, estrogen (ER) status, progesterone (PR) status, second primary cancers, laterality, and American Joint Committee on Cancer staging. Variables from the UPDB included: education, baseline body mass index, baseline Charlson Comorbidity Index (from the International Classification of Disease [ICD] diagnosis codes), family history of breast cancer, family history of cardiovascular disease, and tobacco use (from ICD diagnosis codes).

The primary CVD outcome measures were identified by available ICD coding, specifically, ICD-9 and ICD-10 diagnosis codes through the statewide Ambulatory Surgery database; Inpatient Hospital Claims database from the Utah Department of Health, which includes information on primary, secondary, and additional diagnosis; and hospital discharge information. We also used the electronic medical record (EMR) data from the 2 biggest health care providers in Utah, the University of Utah Health and Intermountain Healthcare. The Clinical Classification Software (CCS) as a part of the International Classification of Diseases (9th Revision) was created by the Healthcare Cost and Utilization Project that collapses over 14,000 diagnosis codes into clinically meaningful categories for the outcome measures.[20] Specifically, as a multi-level hierarchical grouping system, CCS includes 72 cardiovascular outcomes grouped as follows: 1) level 1 (diseases of circulatory system); 2) level 2 (hypertension, diseases of the heart, cerebrovascular diseases, diseases of the arteries, arterioles, capillaries, and diseases of the veins and lymphatics); 3) level 3 (26 outcomes) such as cerebrovascular disease; and 4) level 4 (40 outcomes) such as diseases of the arteries, arterioles, and capillaries (Table 1).

Tobacco users were identified by available ICD-9 diagnosis codes for "tobacco use disorder" (305.1), available ICD-10 diagnosis codes for "nicotine dependence" (F17.200, 21, 22, 29, 201, 203, 208, 209, 210, 211, 213, 218, 219, 220, 221, 223, 228, 229, 290, 291, 293, 298, and F17.299), "tobacco use disorder complicating pregnancy, childbirth, or the puerperium" (99406 and 99407), and available Current Procedural Terminology codes for "tobacco abuse counseling" (Z71.6), "tobacco use" (Z72.0), and "nicotine poisoning" (T65.2), based on the American Academy of Family Physicians coding guidelines.[21] Urban and rural location was classified based on Rural-Urban Continuum Codes from 2013,[22] with the classification scheme that distinguishes metropolitan and nonmetropolitan areas based on county.

Follow-up time was calculated starting from the date of breast cancer diagnosis (index date), the point at which a cancer survivor is considered to be at risk until the first cardiovascular disease incidence or censoring time (last date of follow-up, no outcome, or death). Prevalent cardiovascular disease diagnosis that occurred before the index date were excluded to allow for calculation of incident events (Supporting Table 1). The index date of the breast cancer survivors was assigned to the women matched from the general population to allow for the calculation of follow-up time. A report by the National Association of Health Data Organization on interstate exchange of nonresident data for public health purposes and research, reported that Utah had a small percentage of residents who seek health care outside of the state; specifically, Utah residents discharged in border states ranges from 0.02% in Nevada, 0.08% in Arizona, and 0.13% in Colorado.[23] Similarly, in 2019 the US Census Bureau's state-to-state migration flow, reported fairly low (approximately 3.0%) out-migration rate among Utahns.[24] This

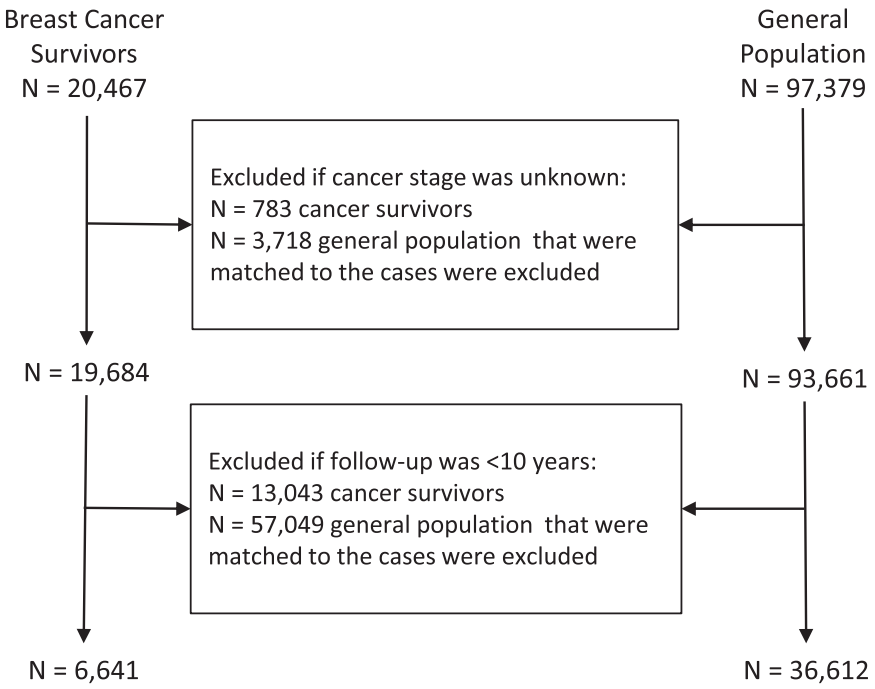

Figure 1. Exclusion criteria for breast cancer survivors and the general population.

allows us to capture nearly the entire diagnosis history of Utah women in our sample.

This study was approved by the University of Utah Institutional Review Board and the Resource for Genetic and Epidemiologic Research, the oversight committee for the UPDB.

Statistical Analysis

Baseline descriptive demographic characteristics between the breast cancer survivors and general population cohorts for categorical variables were compared using Pearson's chi-square (χ^2) tests. To evaluate potential confounders, we assessed the three properties of a confounder. For the association between cancer diagnosis and cardiovascular diseases risk (Table 1), potential confounders that we adjusted on were: baseline Charlson Comorbidity Index (CCI), baseline body mass index (BMI), baseline tobacco use, race, ethnicity. These factors are risk factors for cardiovascular disease, associated with breast cancer diagnosis, and do not act as mediators. Smoking is not considered a strong risk factor for breast cancer, but some recent studies suggest an association.[25] We adjusted on birth year and birth state to account for the matching. For the assessment of risk factors among breast cancer survivors, we adjusted on race and ethnicity, BMI, CCI, baseline tobacco, education, histology, rural residence, age at diagnosis, family history of CVDs, tumor grade, laterality, and diagnosis year, where appropriate. These factors include established and potential risk factors for CVD. The covariates are associated with the exposure of interest and do not act as mediators.

Cox proportional hazards models were used to calculate hazard ratios (HRs) for long-term cardiovascular outcomes from 10 to 15 years, and >15 years after breast cancer diagnosis compared with the women from the general population. We assessed the 10- to 15-year follow-up period, which may interest patients and clinicians to understand the possible risk of CVDs in a 5-year period after reaching 10 years post cancer diagnosis. However, we could not stratify further into the 15- to 20-year period due to the small number of patients for this follow-up time period. Additionally, we assessed risk factors for heart and circulatory system diseases among breast cancer survivors; therefore, we did not use the general population as the comparison group. Ninety-nine percent confidence intervals (CIs) were used to account for multiple testing due to the large number of outcomes (n = 72).[26] Cox proportional hazards models were adjusted for the 2 matching factors, birth state and birth year, and additionally for baseline body mass index (BMI), baseline Charlson Comorbidity Index (CCI), race, and ethnicity. Proportional hazard

TABLE 1. Circulatory System Disease Risk at >10-15 and >15 Years After Cancer Diagnosis in Breast Cancer Survivors in Comparison With a General Population Cohort of Women[a]

Cardiovascular Diseases	>10-15 y			>15 y		
	Patients, No. (%)	General Population, No. (%)	HR (99% CI)	Patients, No. (%)	General Population, No. (%)	HR (99% CI)
7. Diseases of the circulatory system	231 (33.4)	361 (26.2)	1.32 (1.00-1.75)[b]	59 (30.0)	88 (27.0)	0.90 (0.46-1.77)
7.1. Hypertension	375 (14.0)	991 (13.3)	1.07 (0.89-1.30)	138 (14.0)	300 (12.7)	0.90 (0.63-1.41)
7.1.1. Essential hypertension	252 (9.1)	645 (8.3)	0.81 (0.62-1.05)	38 (3.7)	76 (2.9)	0.50 (0.19-1.33)
7.1.2. Hypertension with comp./secondary hypertension	175 (3.0)	521 (2.4)	1.02 (0.76-1.37)	24 (0.9)	85 (1.0)	0.50 (0.17-1.57)
7.3. Cerebrovascular disease	277 (4.9)	836 (4.0)	1.24 (1.00-1.53)[b]	114 (4.8)	319 (4.0)	0.90 (0.54-1.35)
7.3.1. Acute cerebrovascular disease	99 (1.6)	306 (1.3)	1.00 (0.67-1.48)	18 (0.7)	43 (0.5)	0.49 (0.11-2.32)
7.3.2. Occlusion or stenosis of precerebral arteries	61 (1.0)	199 (0.8)	0.82 (0.48-1.39)	13 (0.5)	32 (0.3)	0.70 (0.15-3.48)
7.3.4. Transient cerebral ischemia (transient ischemic attack)	54 (0.9)	226 (1.0)	0.79 (0.48-1.30)	13 (0.5)	32 (0.4)	0.60 (0.13-2.94)
7.4. Diseases of the arteries, arterioles, and capillaries	659 (17.0)	1561 (12.8)	1.42 (1.23-1.64)[b]	259 (17.4)	612 (14.5)	1.08 (0.80-1.44)[b]
7.4.1. Peripheral and visceral atherosclerosis	150 (2.6)	407 (1.8)	1.08 (0.78-1.49)	27 (1.1)	72 (0.8)	0.80 (0.29-1.80)
7.4.2. Aortic, peripheral, and visceral artery aneurysms	36 (0.6)	103 (0.4)	0.96 (0.48-1.94)	—[c] (0.3)	23 (0.2)	1.30 (0.31-5.12)
7.4.3. Aortic and peripheral arterial embolism or thrombosis	11 (0.2)	44 (0.2)	0.65 (0.19-2.20)	—[c] (0.2)	—[c] (0.1)	1.00 (0.06-15.0)
7.4.4.1. Hypotension	185 (3.1)	465 (2.1)	1.13 (0.84-1.54)	30 (1.2)	58 (0.7)	1.40 (0.56-3.33)
7.5. Diseases of the veins and lymphatics	412 (14.1)	900 (11.0)	1.31 (1.09-1.59)	126 (11.8)	256 (10.0)	1.10 (0.71-1.68)
7.2. Diseases of the heart	423 (18.8)	831 (14.6)	1.29 (1.07-1.56)	163 (19.3)	293 (15.3)	1.22 (0.85-1.77)[b]
7.2.1. Heart valve disorders	249 (4.9)	604 (3.3)	0.97 (0.74-1.28)[b]	46 (2.1)	78 (1.1)	0.89 (0.38-2.05)[b]
7.2.2. Peri-, endo-, and myocarditis and cardiomyopathy	111 (1.8)	245 (1.1)	1.30 (0.88-1.93)[b]	30 (1.2)	40 (0.4)	1.77 (0.70-4.44)[b]
7.2.2.1. Cardiomyopathy	78 (1.3)	177 (0.7)	1.34 (0.84-2.14)[b]	19 (0.7)	26 (0.3)	1.08 (0.27-4.83)
7.2.2.2. Other peri-, endo-, and myocarditis	47 (0.8)	99 (0.4)	1.21 (0.64-2.29)[b]	12 (0.5)	20 (0.2)	2.19 (0.65-7.38)
7.2.3. Acute myocardial infarction	63 (1.0)	179 (0.7)	1.02 (0.62-1.68)	—[c] (0.3)	36 (0.4)	0.20 (0.02-2.78)
7.2.4. Coronary atherosclerosis and other heart diseases	186 (3.2)	575 (2.9)	0.94 (0.70-1.24)	40 (1.8)	95 (1.3)	0.79 (0.35-1.83)
7.2.6. Pulmonary heart disease	184 (3.1)	486 (2.2)	1.00 (0.73-1.35)[b]	43 (1.7)	65 (0.8)	1.22 (0.52-2.86)
7.2.8. Conduction disorders	133 (2.2)	380 (1.6)	0.94 (0.66-1.34)	36 (1.4)	69 (0.8)	0.51 (0.16-1.71)
7.2.9. Cardiac dysrhythmias	335 (7.7)	821 (5.7)	0.96 (0.76-1.22)[b]	53 (3.0)	115 (2.2)	0.83 (0.40-1.73)
7.2.10. Cardiac arrest and ventricular fibrillation	38 (0.6)	104 (0.4)	1.28 (0.79-2.01)	—[c] (0.2)	20 (0.2)	0.43 (0.03-6.17)
7.2.11. Congestive heart failure, nonhypertensive	190 (3.3)	489 (2.2)	0.96 (0.71-1.31)	23 (0.9)	66 (0.8)	0.54 (0.16-1.80)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.
BMI imputation estimates for >10-15 y that became insignificant following imputation were observed for cerebrovascular disease (HR, 1.11; 99% CI, 0.92-1.32). Changes in estimates were observed for diseases of the circulatory system (HR, 1.35; 99% CI, 1.08-1.68; HR, 1.30; 99% CI, 1.16-1.47); diseases of the arteries, arterioles, and capillaries (HR, 1.34; 99% CI, 1.19-1.52; HR, 1.28; 99% CI, 1.18-1.39 [using flexible model]); heart valve disorders (HR, 1.36; 99% CI, 1.12-1.65); peri-, endo-, and myocarditis and cardiomyopathy (HR, 1.57; 99% CI, 1.17-2.12), cardiomyopathy (HR, 1.57; 99% CI, 1.10-2.23; HR, 1.76; 99% CI, 1.37-2.26 [using flexible model]); other peri-, endo-, and myocarditis (HR, 1.69; 99% CI, 1.07-2.67; HR, 1.79; 99% CI, 1.30-2.47 [using flexible model]); pulmonary heart disease (HR, 1.27; 99% CI, 1.01-1.60; HR, 1.32; 99% CI, 1.13-1.54 [using flexible model]); and cardiac dysrhythmias (HR, 1.26; 99% CI, 1.06-1.49; HR, 1.36; 99% CI, 1.21-1.52 [using flexible model]) following BMI imputation. BMI imputation estimates that changed for >15 years were observed for diseases of the arteries, arterioles, and capillaries (HR, 1.23; 99% CI, 1.01-1.51); diseases of the heart (HR, 1.31; 99% CI, 1.01-1.70; HR, 1.32; 99% CI, 1.13-1.53 [using flexible model]); heart valve disorders (HR, 1.68; 99% CI, 1.03-2.73; HR, 1.53; 99% CI, 1.12-2.08 [using flexible model], tobacco use estimate was not generated for insufficient observations); and peri-, endo-, and myocarditis and cardiomyopathy (HR, 2.42; 99% CI, 1.28-4.55; HR, 2.44; 99% CI, 1.59-3.75 [using flexible model], tobacco use estimate was not generated for insufficient observations).
[a]Models adjusted for baseline CCI, BMI, baseline tobacco use, race, ethnicity, birth year, and birth state.
[b]Estimates changed when adjusting were made for imputed BMI. Estimates without imputation are reported.
[c]Suppressed because the number was less than 11.

assumption was tested by creating interactions of the predictors and time (survival time) and included in the model. Models in violation of the proportional hazard assumption were tested with flexible parametric modeling with restricted splines and reported where estimates differed. In addition, a modified Cox model was estimated using Fine and Gray's model of competing risks analysis to account for death as a competing outcome rather than censoring those patients who died before experiencing an outcome.[27] When inferences differed between tradition and modified Cox model, the HRs estimates were reported from both models. We also reported risk estimates for CVD outcomes over 10 years for comparison to the 10 to 15 years and over 15 years of

follow-up estimates (Supporting Table 2). Additionally, we performed sensitivity analysis for the CVD risk estimates without including the stage IV breast cancer patients due to the difference in 5-year survival by stage (Supporting Table 3).

Baseline CCI was calculated without cancer to avoid an overestimation of the score calculation. Baseline BMI values were calculated from height and weight information provided in the driver's license records at least 1 year before the breast cancer diagnosis or index date. About 30.2% of missing BMI values were imputed based on cancer diagnosis, baseline CCI, race and age at breast cancer diagnosis using the linear regression model. We estimated the HRs with and without imputation of BMI to assess the impact of imputation. When inferences differed between the 2 models, the HRs without imputed BMI were reported.

The a priori α level used in all statistical analysis was $P < .05$, except as noted, where $P < .01$ was considered statistically significant given the large number of cardiovascular outcomes. Analyses were performed in Statistical Software Package or STATA 15.0 (STATA Inc, College Station, Texas) and Statistical Analysis System software or SAS 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Race, ethnicity, education, family history of breast cancer, family history of cardiovascular disease, and baseline BMI differed between long-term breast cancer survivors and the general population cohorts ($P < .001$; Table 2). Baseline tobacco-use distribution was similar between the 2 groups. The long-term breast cancer survivors had a higher CCI score than women from the general population ($P = .002$).

Approximately 27.7% and 28.4% of the breast cancer patients were diagnosed between 45 to 54 and 55 to 65 years of age, respectively (Table 3). The majority of long-term breast cancer survivors were diagnosed with stage I breast cancer (50.2%) and had ER and PR receptor overexpression (75.6% and 67.5%, respectively). The majority of long-term breast cancer survivors had surgery (99.5%), followed by radiotherapy (55.7%), and chemotherapy (43.9%).

From 10 to 15 years following breast cancer diagnosis, approximately 33.4% of breast cancer survivors had a new diagnosis of diseases of the circulatory system compared with 26.2% of the general population cohort (Table 1). Specifically, from 10 to 15 years of follow-up, breast cancer survivors had a 32% (HR, 1.32; 99% CI, 1.00-1.75; $P = .009$ and HR, 1.31; 99% CI, 0.99-1.73; $P = .011$ using competing risks model) higher risk of diseases of the circulatory system, 42% (HR, 1.42; 99% CI, 1.23-1.64 and HR, 1.39; 99% CI, 1.20-1.61 using competing risks model) higher risk of diseases of the arteries, arterioles, and capillaries, 24% (HR, 1.24; 99% CI, 1.00-1.53; $P = .009$ and HR, 1.19; 99% CI, 0.96-1.48; $P = .035$ using competing risks model) higher risk

TABLE 2. Demographic Characteristics Among 10-Year Breast Cancer Survivors and the General Population

Characteristics	Breast Cancer, No. % (N = 6641)	General Population, No. % (N = 36,612)	P[a]
Birth year			
<1930	760 (11.4)	3856 (10.5)	.001
1930-1939	1166 (17.6)	6107 (16.7)	
1940-1949	1894 (28.5)	10,134 (27.7)	
1949-1959	1856 (28.0)	10,733 (29.3)	
>1960	965 (14.5)	5782 (15.8)	
Race			
White	6339 (95.5)	34,690 (94.8)	<.0001
Black	11 (0.2)	86 (0.2)	
Asian	77 (1.2)	304 (0.8)	
Pacific Islander	14 (0.2)	70 (0.2)	
American Indian/ Alaskan Native	—[b] (0.1)	167 (0.5)	
Multiracial	190 (2.8)	701 (1.9)	
Unknown	—[b] (0.0)	594 (1.6)	
Hispanic			
Yes	596 (9.0)	2700 (7.4)	<.0001
No	6045 (91.0)	33,912 (92.6)	
Education			
High school or less	940 (14.2)	5148 (14.1)	<.0001
High school	2192 (33.0)	12,423 (33.9)	
Some college	1945 (29.2)	11,178 (30.5)	
College	921 (13.9)	5025 (13.7)	
Beyond college	643 (9.7)	2838 (7.8)	
Baseline BMI (kg/m^2)[c]			
<18.5	91 (2.0)	762 (2.1)	<.0001
18.5-24.9	2246 (48.7)	14,392 (40.3)	
25.0-29.0	1446 (31.3)	11,603 (32.4)	
>30.0	833 (18.1)	8991 (25.2)	
Baseline CCI			
0	4869 (73.3)	27,593 (75.4)	.002
1	1186 (17.9)	6056 (16.5)	
≥2	586 (8.8)	2963 (8.1)	
Family history of breast cancer[d]			
Yes	2929 (44.1)	15,378 (42.0)	.001
No	3712 (55.9)	21,234 (58.0)	
Family history of CVD[d]			
Yes	4237 (63.8)	25,539 (69.8)	<.0001
No	2404 (36.2)	11,073 (30.2)	
Baseline tobacco use			
Yes	242 (3.6)	1363 (3.7)	.80
No	6399 (96.4)	35,249 (96.3)	

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence Interval; CVD, cardiovascular disease; HR, hazard ratio.
[a]Two-sided Pearson's χ^2 test.
[b]Suppressed because the number was less than 11.
[c]Total missing BMI, n = 2889 (6.8%): 2025 (4.7%) of the breast cancer survivors and 864 (2.0%) of the general population had missing BMI values.
[d]In first-, second-, and third-degree relatives.

of cerebrovascular disease, and 31% (HR, 1.31; 99% CI, 1.09-1.59 and HR, 1.29; 99% CI, 1.06-1.56 using competing risks analysis) higher risk of diseases of the veins and lymphatics compared with the women from the general population, adjusting for baseline CCI, BMI, tobacco use, race, ethnicity, birth year, and birth state. When we compared the risk estimates adjusting for the original BMI variable versus imputed BMI, the estimates for heart valve disorders, cardiomyopathy, and pulmonary heart disease were significant only when adjusting for imputed BMI as specified in the footnotes (Table 1). Thus, in the tables, the estimates without BMI imputations were reported. Overall, no associations were observed for any cardiovascular diseases after more than 15 years of follow-up (Table 1).

From 10 to 15 years of follow-up, 18.8% of breast cancer survivors had a diagnosis of diseases of the heart compared with 14.6% of women from the general population (Table 1). From >10 to 15 years of follow-up, breast cancer survivors had a 29% (HR, 1.29; 99% CI, 1.07-1.56 and HR, 1.27; 99% CI, 1.05-1.55 using competing risks analysis) higher risk of diseases of the heart compared with the women from the general population, adjusting for baseline CCI, BMI, tobacco use, race, ethnicity, birth year, and birth state. However, we did not observe an increase in risk in any of the specific heart diseases such as cardiomyopathy, myocardial infarction or congestive heart failure in this cohort of long-term breast cancer survivors. Consistent with the primary analysis, most risk estimates for >10 to 15 years of follow-up in breast cancer survivors compared with the general population were similar for >10 years of follow-up (Supporting Table 2). When restricted to women diagnosed with stage I-III breast cancer, increased CVD risks were observed in the >10 to 15 years of follow-up period among breast cancer survivors compared with the general population (Supporting Table 3). Although the overall circulatory system disease risk was no longer statistically significant for stage I-III breast cancer patients, the HRs for the other CVDs did not change our inferences. Consistent with the primary analysis, no associations were observed for any CVDs for >15 years of follow-up in the sensitivity analysis (Supporting Table 3).

Among breast cancer survivors, baseline and demographic risk factors were assessed for diseases of the heart and the circulatory system diagnosed after 10 years of follow-up (Table 4). Older age, lower education level (some high school or less), family history of cardiovascular diseases, and family history of breast cancer were observed as risk factors for both diseases of the heart and of the circulatory system among long-term breast cancer survivors. Baseline CCI was a risk factor for diseases of the circulatory system, whereas baseline BMI (>30 kg/m^2) and White race were risk factors for diseases of the heart.

TABLE 3. Clinical Characteristics Among 10-Year Breast Cancer Survivors Diagnosed in 1997-2009 (N = 6641)

Characteristics	No. (%)
Age at cancer diagnosis (y)	
19-45	1057 (15.9)
45-54	1837 (27.7)
55-64	1889 (28.4)
65-74	1303 (19.6)
75-95	555 (8.4)
Surgery	
Yes	6608 (99.5)
No	33 (0.5)
Chemotherapy	
Yes	2916 (43.9)
No	3597 (54.2)
Unknown	128 (1.9)
Radiotherapy	
Yes	3699 (55.7)
No	2861 (43.1)
Unknown	81 (1.2)
Endocrine therapy	
Yes	2022 (30.4)
No	4427 (66.7)
Unknown	192 (2.9)
Tumor grade[d]	
Grade I	1396 (21.0)
Grade II	2788 (42.0)
Grade III/IV	2083 (31.4)
Unknown\not stated	374 (5.6)
ER status[a]	
Positive	5017 (75.6)
Negative	1262 (19.0)
Unknown	362 (5.4)
PR status[a]	
Positive	4481 (67.5)
Negative	1732 (26.1)
Unknown	428 (6.4)
Laterality	
Right	3257 (49.0)
Left	3384 (51.0)
Second primary[b]	
Yes	972 (14.6)
No	5669 (85.4)
AJCC staging	
I	3333 (50.2)
II	2701 (40.7)
III	510 (7.7)
IV	97 (1.4)
Rural residence[c]	
Yes	671 (10.1)
No	5970 (89.9)

Abbreviations: AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; RUCC, Rural-Urban Continuum Code.
[a]HER2 for cancer subtype characterization was not available until 2010.
[b]Breast cancer patients with breast cancer as first of 2 or more primary cancers.
[c]Residence was classified according to 2013 RUCCs.
[d]Tumor Grade IV, n = 54 (0.8%).

TABLE 4. Demographic and Baseline Risk Factors of Diseases of the Heart and Circulatory System 10 Years After Breast Cancer Diagnosis

Risk Factors	Diseases of the Heart, HR (95% CI)	Diseases of the Circulatory System, HR (95% CI)
Age at cancer diagnosis (y)[a]		
19-45	REF	REF
45-54	1.32 (0.91-1.92)	1.18 (0.79-1.75)
55-64	2.06 (1.43-2.97)	1.78 (1.18-2.70)
65-74	2.58 (1.72-3.86)	2.01 (1.14-3.53)
75-95	4.20 (2.55-6.91)	4.01 (1.72-9.35)
P for trend	<.0001	<.0001
Baseline BMI (kg/m^2)[b]		
<18.5	0.51 (0.19-1.38)	0.77 (0.36-1.67)
18.5-24.9	REF	REF
25.0-29.0	1.20 (0.95-1.52)	1.02 (0.71-1.47)
>30.0	1.62 (1.22-2.14)	1.07 (0.61-1.86)
P for trend	<.0001	<.0001
Baseline CCI[b]		
0	REF	REF
1	1.10 (0.86-1.42)	1.03 (0.66-1.60)
≥2	1.34 (0.80-2.25)	2.64 (1.08-6.45)
P for trend	<.0001	<.0001
Education[c]		
High school or less	1.41 (1.29-1.54)	1.28 (1.15-1.42)
High school	REF	REF
Some college	0.89 (0.83-0.96)	1.00 (0.93-1.08)
College	0.80 (0.73-0.88)	0.99 (0.99-1.09)
Beyond college	0.81 (0.72-0.90)	0.85 (0.75-0.95)
Baseline tobacco use[d]		
No	REF	REF
Yes	0.93 (0.74-1.16)	1.06 (0.82-1.39)
Race[e]		
White	REF	REF
Other	0.74 (0.65-0.84)	0.76 (0.67-0.86)
Hispanic[e]		
No	REF	REF
Yes	1.12 (1.01-1.24)	0.97 (0.86-1.09)
Family history of CVD[f]		
No	REF	REF
Yes	1.24 (1.16-1.32)	1.19 (1.11-1.27)
Family history of breast cancer[f]		
No	REF	REF
Yes	1.19 (1.13-1.27)	1.11 (1.04-1.18)
Rural residence[f]		
Urban	REF	REF
Rural	0.80 (0.63-1.01)	0.83 (0.61-1.12)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; REF, reference.
[a]Model adjusted for BMI, CCI, race/ethnicity, baseline tobacco use, education, and histology.
[b]Model adjusted for race/ethnicity, baseline tobacco use, education, rural residence, age at diagnosis, and family history of CVD.
[c]Model adjusted for race/ethnicity, and rural residence.
[d]Model adjusted for race/ethnicity, education, and rural residence.
[e]Model adjusted for rural residence.
[f]Model adjusted for race/ethnicity.

TABLE 5. Clinical Risk Factors for Diseases of the Heart and Circulatory System 10 Years After Breast Cancer Diagnosis

Risk Factors	Diseases of the Heart, HR (95% CI)	Diseases of the Circulatory System, HR (95% CI)
Diagnosis year (y)[a]		
1997-2001	REF	REF
2002-2005	0.95 (0.75-1.21)	0.95 (0.69-1.33)
2006-2009	0.87 (0.63-1.20)	0.72 (0.46-1.13)
Surgery[b]		
No	REF	REF
Yes	1.62 (0.22-11.8)	0.06 (0.01-0.60)
Chemotherapy[b]		
No	REF	REF
Yes	1.24 (0.99-1.57)	1.17 (0.86-1.60)
Radiotherapy[b]		
No	REF	REF
Yes	1.18 (0.95-1.47)	1.20 (0.89-1.62)
Endocrine therapy[b]		
No	REF	REF
Yes	1.25 (0.99-1.57)	1.40 (1.00-1.95)
Endocrine receptor status[c]		
ER+ and/or PR+	REF	REF
ER– and/or PR–	0.98 (0.74-1.30)	1.12 (0.79-1.59)
Second primary[d,f]		
No	REF	REF
Yes	1.32 (0.99-1.77)	1.59 (1.00-2.52)
Tumor grade[e]		
Grade I	REF	REF
Grade II	1.04 (0.80-1.37)	1.26 (0.83-1.92)
Grade III	0.92 (0.69-1.24)	0.93 (0.59-1.47)
AJCC stage[e]		
I	REF	REF
II	1.00 (0.81-1.24)	1.20 (0.88-1.62)
III	0.95 (0.58-1.57)	0.85 (0.41-1.78)
IV	1.53 (0.78-3.02)	1.64 (0.79-3.45)

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; REF, reference.
[a]Models adjusted for BMI, CCI, race/ethnicity, baseline tobacco use, education, and age at diagnosis.
[b]Models adjusted for BMI, CCI, race/ethnicity, education, rural residence, tumor grade, laterality, diagnosis year, and age at diagnosis.
[c]Models adjusted for BMI, CCI, race/ethnicity, baseline tobacco use, and age at diagnosis.
[d]Models adjusted for BMI, CCI, race/ethnicity, baseline tobacco use, education, rural residence, tumor grade, age at diagnosis, family history of breast cancer, endocrine therapy, chemotherapy, and radiotherapy.
[e]Models adjusted for BMI, CCI, race/ethnicity, baseline tobacco use, diagnosis year, and age at diagnosis.
[f]Breast cancer patients with breast cancer as first of 2 or more primary cancers.

Clinical characteristics and breast cancer treatments were not associated with either diseases of the heart or the circulatory system among long-term breast cancer survivors (Table 5). Breast cancer survivors with second or multiple primary cancers had a 59% higher risk (*P* value = .05) of the circulatory system disease compared with women that had breast cancer as one primary in their lifetime (Table 5).

DISCUSSION

Long-term breast cancer survivors had a higher risk of diseases of the circulatory system, diseases of the arteries, arterioles, and capillaries, diseases of the veins and lymphatics, and diseases of the heart when compared with the general population cohort in the follow-up

period of >10 to 15 years. However, the risk did not differ by diagnosis year, tumor stage, tumor grade, and breast cancer treatments among this cohort of long-term breast cancer survivors. With a longer follow-up of >15 years, breast cancer survivors did not have a higher risk of CVD outcomes in comparison to the general population. Long-term breast cancer survivors were more likely to have a higher CCI score and family history of breast cancer than women from the general population.

In terms of overall incident CVDs, we observed a 33% higher risk of diseases of the circulatory system and 19% higher risk of diseases of the heart among long-term breast cancer survivors compared with the general population in the follow-up period of >10 to 15 years. Large-scale population-based studies of breast cancer survivors comparing CVD risks in breast cancer survivors to general population cohorts have been inconsistent. Some reported an increased or moderate CVD risk,[7-9,12] whereas others reported no increased CVD risk for breast cancer patients compared to the general population.[10,11] However, most of these studies did not examine the period beyond 10 years of follow-up. Khan et al included breast cancer survivors who survived at least 5 years (10.2 mean years of follow-up from cancer diagnosis) and reported an elevated incidence of congestive heart failure and coronary artery disease compared with the general population.[5,8] In contrast, a study from the Netherlands by Schoormans et al observed no increased CVD risk within 8-13 years following diagnosis among 6762 breast cancer survivors compared to 6762 cancer-free women from the general population.[7,10] In a study of 2535 breast cancer patients, most of whom were identified in the Cancer Genetics Network, Hill et al observed no increased risk for heart disease for >10 years after cancer diagnosis compared with the general population.[8,11] A possible explanation for the difference in risk estimations from the Schoormans et al and Hill et al studies may be that our results,[7,8] as well as those from the Khan et al study,[5] are based on medical records rather than patient self-report data. Previous studies have shown that patients may confuse various CVD diagnoses, and 30% of self-reported cardiovascular outcomes were misclassified by patients.[28]

In the follow-up period of more than 15 years, we did not observe a higher risk for CVD outcomes in breast cancer survivors compared with the general population. There were 2929 breast cancer survivors and 17,168 women from the general population within the >15 years of follow-up period (163 heart disease diagnoses in breast cancer survivors vs. 293 heart disease diagnoses in the general population). Although it is possible that we did not detect any associations in the 15-year follow-up because of lower statistical power, our results also support the possibility that CVD risk becomes similar over time in breast cancer survivors and women from the general population. To our knowledge, our study is the first to report on CVD risk estimates for long-term breast cancer survivors for 15 or more years after cancer diagnosis compared to cancer-free women from the general population.

In terms of CVD risk factors among long-term breast cancer survivors in our study, the predictors for both heart diseases and circulatory system diseases were older age, obesity, family history of CVDs, family history of breast cancer, and low education. Baseline CCI was a risk factor for diseases of the circulatory system. Older age have also been shown in other studies to be risk factors for heart disease or hospitalization in early-stage breast cancer[4] or congestive heart failure following trastuzumab, but were assessed at 10 years of follow-up.[19] Another long-term study among breast cancer survivors diagnosed between 1958 and 2001 reported that patients with higher BMI, diabetes, or presence of other CVDs had higher rates of major coronary events following radiotherapy in right- versus left-treated tumors after 10 years of follow-up.[11]

In our study, we did not observe an association between radiotherapy, chemotherapy, or endocrine therapy with the late-onset CVDs among this cohort of long-term breast cancer survivors. For radiotherapy treatment, we did not observe an increased risk of heart and circulatory system diseases. Previously, 1 long-term study among breast cancer patients reported an increased rate of major coronary events within 10 to 19 and >20 years,[14] and another study reported an increase in incidence of all heart disease after 10 to 14 and >15 years[29] following radiation in women with left- versus right-breast cancers. Our risk estimate for heart disease among patients receiving radiation therapy was not statistically significant but suggestive of an association (HR, 1.18; 95% CI, 0.95-1.47); we may have lacked statistical power to detect the risk because we focused on the long-term survivors who had smaller numbers of heart disease events. Similarly, the lack of association maybe explained by improvements in radiotherapy techniques over time that have contributed to reducing radiation exposure to the heart.

A major strength of our study is that we were able to assess a comprehensive list of cardiovascular disease outcomes over long-term follow-up in a large sample size of 6641 breast cancer patients. We also had a large

comparison group of 36,612 women without cancer from the general population who were matched on birth year and birth state. The population-based design and inclusion of all women diagnosed with breast cancer in Utah identified by the Utah Cancer Registry during the study period minimizes potential selection bias. Furthermore, our assessment of outcomes is based on electronic medical records from 2 of the largest medical care providers in Utah and the statewide hospital ambulatory surgery and discharge records and are not subject to recall bias. Although our study may miss less severe cardiovascular diagnoses, the available ICD diagnosis codes in our study allow us to capture severe cases. The high proportion of breast cancer patients followed up over the study minimizes survival bias that is an issue for survivorship studies relying on self-reported outcomes. Within 5 years following a cancer diagnosis, increased medical surveillance may result in a bias away from the null. However, our study is based on breast cancer patients starting at 10 years after cancer diagnosis, thus surveillance bias should be minimized.

This study had some limitations. Utah is becoming more diverse, and 9% of the breast cancer patients in our sample were Hispanic. However, our cohort of breast cancer survivors and the general population did not have a strong representation of other race and ethnicity groups. Thus, our study results may not be generalizable to other more diverse states. More detailed cancer treatment information, especially chemotherapy agents and related dosage, was not available in our study and could help further explain differences in risk across specific cardiovascular diseases among breast cancer patients. Similarly, we may not have captured the majority of breast cancer patients receiving extended endocrine therapy beyond 5 years to detect late-cardiac effects. However, endocrine therapy use in this cohort may be underrepresented, and therefore is likely to underestimate or bias toward to the null the long-term cardiac risk in this cohort of breast cancer survivors. In addition, we were unable to identify patients with cancer recurrence who would have initiated additional treatments that could influence development of additional CVD outcomes. However, we evaluated whether breast cancer patients with second or multiple primaries had higher risks of CVDs (Table 5). Furthermore, developing methods to obtain more detailed treatment information and recurrence from the EMR and claims databases would be a future direction of research. Data on the expression of human epidermal growth factor receptor 2 was unavailable until 2010, although ER and PR receptor expression status was available for this cohort of long-term breast cancer survivors.

Although we were able to assess cardiovascular disease outcomes for >15 years of follow-up, there were fewer breast cancer survivors in the >15-year follow-up period, which may explain why some possible associations were not detected for the later time period. Similarly, we may have lacked statistical power to detect an association for specific diseases of the heart such as congestive heart failure or myocardial infarction (<100 observations). Although there is a potential for poorly ascertained cardiovascular diagnoses codes by ICD coding, administrative ICD-9 diagnosis codes for heart failure and related comorbidities had 95% specificity and 93% positive predictive value.[30] Any coding errors may result in nondifferential misclassification or underestimation of the risk estimate. However, we observed higher risks in breast cancer survivors than in the general population cohort.

In summary, increased risk of cardiovascular diseases, namely heart diseases, diseases of the arteries, arterioles, capillaries, and diseases of veins and lymphatics, was observed among long-term breast cancer survivors compared with the matched general population cohort. However, for patients followed beyond 15 years after diagnosis, increased risks of any cardiovascular diseases were not observed for breast cancer survivors compared to the general population. Our findings highlight the importance of survivorship care, with monitoring and intervention for a broader spectrum of cardiovascular diseases, following breast cancer for survivors at increased risk. Furthermore, factors affecting cardiovascular diseases in this study, such as higher BMI, may suggest opportunities for cardiovascular disease prevention in breast cancer patients during and years following treatment.

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Benjamin Adam Haaland received consulting fees from Astra Zeneca, the National Kidney Foundation, Prometics Life Sciences, and Value Analytics Labs; has received travel funds from Flatiron Health; and has served as a

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AUTHOR CONTRIBUTIONS

Alzina Koric: Conceptualization, formal analysis, and writing–original draft. **Bayarmaa Mark:** Data preparation and biostatistical support. **Chun-Pin Chang:** Data acquisition and method development. **Kerry Rowe:** Data acquisition and method development. **John Snyder:** Data acquisition and method development. **Mark Dodson:** Data acquisition and method development. **Vikrant G. Deshmukh:** Data acquisition and method development. **Michael G. Newman:** Data acquisition and method development. **Alison M. Fraser:** Data acquisition and method development. **Ken R. Smith:** Data acquisition and method development. **Ankita P. Date:** Data acquisition and method development. **Lisa H. Gren:** Critical review of manuscript. **Benjamin A. Haaland:** Critical review of manuscript. **Christina A. Porucznik:** Critical review of manuscript. **N. Lynn Henry:** Critical review of manuscript. **Mia Hashibe:** Review, conceptualization, funding acquisition, and final approval of manuscript.

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