

Risk of Cardiovascular Diseases Among Older Breast Cancer Survivors in the United States: A Matched Cohort Study

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ABSTRACT

Background: It has been suggested that cardiovascular risks are increased in breast cancer survivors, but few studies have quantified the risks of a range of specific clinically important cardiovascular outcomes in detail. **Patients and Methods:** Women aged >65 years with incident breast cancer from 2004 to 2013 in the SEER-Medicare linked database were matched with 5 cancer-free female counterparts (5:1 ratio). Prevalence of specific cardiovascular outcomes at baseline was measured, then Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals for the risk of individual cardiovascular outcomes during follow-up. Modification of the effect was investigated by time since diagnosis, race/ethnicity, prior cardiovascular disease (CVD), and age. **Results:** In all, 91,473 women with breast cancer and 454,197 without breast cancer were included. Women with breast cancer had lower baseline prevalence of all CVDs. Compared with cancer-free controls, breast cancer survivors had substantially increased risks of deep vein thrombosis (adjusted HR, 1.67; 95% CI, 1.62–1.73; 386,484 person-years of follow-up) and pericarditis (HR, 1.43; 95% CI, 1.38–1.49; 390,776 person-years of follow-up); evidence of smaller increased risks of sudden cardiac arrest, arrhythmia, heart failure, and valvular heart disease (adjusted HRs ranging from 1.05–1.09, lower CI limits all ≥ 1); and evidence of lower risk of incident angina, myocardial infarction, revascularization, peripheral vascular disease, and stroke (adjusted HRs ranging from 0.89–0.98, upper CI limits all ≤ 1). Increased risks of arrhythmia, heart failure, pericarditis, and deep vein thrombosis persisted >5 years after cancer diagnosis. **Conclusions:** Women with a history of breast cancer were at increased risk of several CVDs, persisting into survivorship. Monitoring and managing cardiovascular risk throughout the long-term follow-up of women diagnosed with breast cancer should be a priority.

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Background

Breast cancer remains the most common cancer among women worldwide. Earlier detection and the advent of new treatments have facilitated an increase in 5-year survival rate in the United States from 75% in the 1970s to 91% in the 2010s.¹ In older women diagnosed with breast cancer, there is now a greater likelihood of dying of diseases other than cancer itself. Cardiovascular disease (CVD) is the most frequent cause of noncancer-related death,^{2,3} and there are concerns that overlapping risk factors and cardiotoxicities associated with cancer treatments may increase cardiovascular risk in this population.

There have been few large studies that have assessed the burden of specific CVDs in breast cancer survivors, with most studies focusing on composite cardiovascular outcomes.^{4–13} Before attempting to fully understand the mechanisms behind changes in cardiovascular risk in women diagnosed with breast cancer, there is a pressing need for evidence on associations between breast cancer and clinically specific cardiovascular outcomes. This will pave the way for further exploration of the treatments and risk factors that cause any changes in risk of specific CVDs.

We therefore assessed the prevalence of a range of clinically specific cardiovascular outcomes at breast cancer diagnosis and their incidence after diagnosis among survivors aged >65 years compared with similar women without cancer in the United States.

Patients and Methods

Study Design and Data Source

We performed a matched cohort study using prospectively collected data from the SEER-Medicare linked claims-based database. The SEER cancer surveillance program currently covers approximately 35% of the US population.¹⁴ Medicare Parts A and B provide US government-funded inpatient, physician, and outpatient



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health insurance for individuals aged ≥ 65 years¹⁵ and those aged < 65 years with specific disabilities. The SEER-Medicare database is linked using a deterministic algorithm based on name, social security number, sex, and date of birth.

Study Population

We identified all women aged > 65 years with an incident stage I–III breast cancer diagnosis in 2004 through 2013. Patients were required to have 1 year of continuous Medicare Parts A and B coverage prior to their diagnosis date to ensure included diagnosis codes reflected incident rather than prevalent CVD. Each patient with breast cancer was matched at diagnosis on year of birth, SEER region (Northeast, South, North Central, West), and race/ethnicity (White, Black, Asian, Hispanic, Native American, other) to up to 5 women with replacement from the 5% SEER-Medicare noncancer sample who were free of any cancer at the time of their matched patient's diagnosis date (diagnosis date and matched date for the comparison cohort are hereafter referred to as "index date"). Women were excluded if they were diagnosed with any other cancer prior to their index date (excluding nonmelanoma skin cancer).

Exposures

The main exposure was a diagnosis of breast cancer. Women diagnosed with cancer were compared with a matched noncancer comparison cohort of women.

Outcomes

The main cardiovascular outcomes of interest were coronary artery disease (angina, myocardial infarction, revascularization procedures, sudden cardiac arrest), peripheral vascular disease, stroke, arrhythmia, heart failure, pericarditis, valvular heart disease, and venous thromboembolism (deep vein thrombosis [DVT], pulmonary embolism). Composite cardiovascular outcomes and individual components of composite outcomes were analyzed separately. Events were identified through a claim with ICD-9 diagnosis and procedure or HCPCS procedure codes in any position (see supplemental eTable 1, available with this article at JNCCN.org).

Covariates

The following covariates were extracted at index date: age (66–75, > 75 –85, > 85 years), hypertension, diabetes, chronic kidney disease, rheumatoid arthritis, time since index date (0–1 year, 1–3 years, 3–5 years, ≥ 5 years), and current year. Information on cancer stage, grade, and estrogen receptor (ER) or progesterone receptor (PR) status (a record of ER-positive or PR-positive disease indicated a patient was ER/PR-positive) was also extracted for women diagnosed with breast cancer.

All comorbidities were defined during the 1-year period prior to index date and were based on the Klabunde adaptation of the Charlson comorbidity index,¹⁶ which searches across patients' inpatient and outpatient claims to retain diagnosis codes that are either in the inpatient setting or in 2 outpatient visits separated by > 30 days.

Statistical Analysis

The distribution of all covariates at index date between women diagnosed with breast cancer and their cancer-free comparisons was described, including the prevalence of all cardiovascular outcomes in the year before index date. Composite and individual cardiovascular outcomes were analyzed separately. Women diagnosed with the specific cardiovascular outcomes of interest within the year prior to index date were excluded from the analysis of that outcome to ensure incident disease was being measured during follow-up (these were the women previously used to calculate prevalent disease for each cardiovascular outcome at index date). Follow-up began 90 days after index date, because preliminary analyses suggested an acute increased risk of all cardiovascular outcomes in breast cancer survivors compared with their noncancer comparisons during the first 90 days after diagnosis, which is likely caused by women engaging with the healthcare system at the time of their diagnosis and retrospective recording of prevalent CVD (see supplemental eTable 2 for detailed time-stratified analyses). Follow-up ended at earliest of disenrollment from Medicare Parts A or B, death, end of follow-up (December 12, 2014), or the date of cardiovascular outcome of interest.

Primary Analyses

Number of events and crude incidence rates for each outcome of interest were calculated for women diagnosed with breast cancer and their matched comparisons, along with resulting rate differences. Associations between breast cancer and cardiovascular outcomes were then explored in unadjusted (accounting for matching variables) and adjusted (accounting for all other covariates described above, excluding breast cancer-specific covariates) Cox proportional hazards regression models stratified by matched set (1 model per outcome), with an underlying age timescale. Women with missing data for any covariate ($< 1\%$ overall) were excluded (complete-case analysis).

Modification of the effect of breast cancer on cardiovascular risk by the following variables was investigated by fitting interaction terms: time since index date (0–1, 1–3, 3–5, ≥ 5 years), race/ethnicity (White, Black, Asian, Hispanic, Native American, other), any cardiovascular disease prior to index date, and age (66–75, > 75 –85, > 85 years). The role of cancer stage,

Table 1. Baseline Characteristics of Study Cohorts

	Noncancer n (%)	Breast Cancer n (%)	Total n (%)
Total, N	454,197 (100)	91,473 (100)	545,670 (100)
Age^a			
66–75 y	218,687 (48.1)	44,005 (48.1)	262,692 (48.1)
>75–85 y	177,740 (39.1)	35,729 (39.1)	213,469 (39.1)
>85 y	57,770 (12.7)	11,739 (12.8)	69,509 (12.7)
Median (IQR)	75 (70–81)	75 (70–81)	75 (70–81)
Race/Ethnicity^a			
White	394,263 (86.8)	78,937 (86.3)	473,200 (86.7)
Black	35,544 (7.8)	7,233 (7.9)	42,777 (7.8)
Other	8,261 (1.8)	1,773 (1.9)	10,034 (1.8)
Asian	10,328 (2.3)	2,145 (2.3)	12,473 (2.3)
Hispanic	4,879 (1.1)	1,074 (1.2)	5,953 (1.1)
Native American	742 (0.2)	212 (0.2)	954 (0.2)
Missing	180 (0)	99 (0.1)	279 (0.1)
SEER region^a			
Northeast	90,577 (19.9)	18,187 (19.9)	108,764 (19.9)
South	114,436 (25.2)	23,037 (25.2)	137,473 (25.2)
North Central	54,951 (12.1)	11,063 (12.1)	66,014 (12.1)
West	190,962 (42)	38,438 (42)	229,400 (42)
Missing	3,271 (0.7)	748 (0.8)	4,019 (0.7)
Cancer stage			
I	—	50,716 (55.4)	—
II	—	30,772 (33.6)	—
III	—	9,985 (10.9)	—
Missing	—	0 (0)	—
Grade			
1	—	22,813 (24.9)	—
2	—	39,761 (43.5)	—
3	—	23,701 (25.9)	—
Missing	—	5,198 (5.7)	—
ER/PR status			
Positive	—	74,595 (81.5)	—
Negative	—	12,442 (13.6)	—
Missing	—	4,436 (4.8)	—
Rheumatoid arthritis before index date	12,729 (2.8)	2,121 (2.3)	14,850 (2.7)
Chronic kidney disease before index date	16,255 (3.6)	3,045 (3.3)	19,300 (3.5)
Hypertension before index date	211,795 (46.6)	44,716 (48.9)	256,511 (47)
Diabetes before index date	85,652 (18.9)	18,459 (20.2)	104,111 (19.1)
Prevalence of CVD before index date^b			
Coronary artery disease	24,735 (5.4)	4,478 (4.9)	29,213 (5.4)
Angina	21,736 (4.8)	4,077 (4.5)	25,813 (4.7)
Myocardial infarction	4,502 (1.0)	642 (0.7)	5,144 (0.9)
Revascularization	4,208 (0.9)	673 (0.7)	4,881 (0.9)
Sudden cardiac arrest	741 (0.2)	79 (0.1)	820 (0.2)

(continued on next page)

Table 1. Baseline Characteristics of Study Cohorts (cont.)

	Noncancer n (%)	Breast Cancer n (%)	Total n (%)
Prevalence of CVD before index date (cont.) ^b			
Peripheral vascular disease	33,381 (7.3)	6,063 (6.6)	39,444 (7.2)
Stroke	35,534 (7.8)	6,351 (6.9)	41,885 (7.7)
Arrhythmia	54,834 (12.1)	11,110 (12.1)	65,944 (12.1)
Heart failure	57,771 (12.7)	10,738 (11.7)	68,509 (12.6)
Pericarditis	2,092 (0.5)	412 (0.5)	2,504 (0.5)
Valvular heart disease	58,674 (12.9)	11,683 (12.8)	70,357 (12.9)
Venous thromboembolism	4,180 (0.9)	788 (0.9)	4,968 (0.9)
Deep vein thrombosis	3,875 (0.9)	736 (0.8)	4,611 (0.8)
Pulmonary embolism	379 (0.1)	64 (0.1)	443 (0.1)

Abbreviations: CVD, cardiovascular disease; ER, estrogen receptor; IQR, interquartile range; PR, progesterone receptor.

^aMatching variables.

^bOne year before index date.

grade, and ER/PR receptor status was also explored by subdividing those diagnosed with breast cancer according to their stage, grade, and ER/PR status, and estimating separate hazard ratios (HRs) for each group.

Flexible Parametric Models

To model differing effects of a breast cancer diagnosis on cardiovascular risk over time, flexible parametric survival models were built for each outcome, using time since index date as the timescale.¹⁷ These models used cubic splines to model the cumulative hazard, allowing for the specification of time-dependent covariate effects. All models used a spline with 3 knots placed at 1, 3, and 5 years after index date, and were adjusted for all covariates.

Sensitivity Analyses

Primary analyses were repeated using only inpatient claims to define cardiovascular outcomes, which may be more reliable when defining incident outcomes in comparison with outpatient claims.

Results

A total of 545,670 women aged >65 years were included in the study population: 91,473 (17%) with a breast cancer diagnosis and 454,197 (83%) without cancer (Table 1). The comorbidity profile of these women was generally similar, with those diagnosed with breast cancer having a slightly higher prevalence of hypertension and diabetes at diagnosis compared with their noncancer counterparts. The prevalence of all CVDs was slightly lower in women diagnosed with breast cancer, but differences were generally small.

Primary Analyses

Mean follow-up per person ranged from 3.73 years in the valvular heart disease analysis to 4.50 years in the

pulmonary embolism analysis. Incident rates of cardiovascular outcomes in those diagnosed with breast cancer ranged from 0.89 events per 1,000 person-years in the pulmonary embolism analysis to 80.74 events per 1,000 person-years in the arrhythmia analysis (Table 2). In the noncancer comparisons, incident rates ranged from 0.86 per 1,000 person-years in the pulmonary embolism analysis to 74.98 per 1,000 person-years in the arrhythmia analysis (Table 2). After adjustment for all covariates and excluding the first 90 days of follow-up, there was evidence of a slightly lower risk of angina, myocardial infarction, revascularization, peripheral vascular disease, and stroke in women diagnosed with breast cancer compared with the matched comparison cohort (Table 2). Adjusted HRs ranged from 0.89 (95% CI, 0.85–0.92) for revascularization to 0.98 (95% CI, 0.97–1.00) for stroke. There was evidence of an increased risk of sudden cardiac arrest, arrhythmia, heart failure, pericarditis, valvular heart disease, and DVT in women diagnosed with breast cancer compared with the noncancer cohort. Adjusted HRs ranged from 1.05 (95% CI, 1.01–1.10) for sudden cardiac arrest to 1.67 (95% CI, 1.62–1.73) for DVT.

Variation Over Time and Effect Measure Modification

There was evidence of effect measure modification by time since index date for all outcomes except pulmonary embolism (Table 3). A breast cancer diagnosis was associated with a lower risk of angina, myocardial infarction, revascularization, peripheral vascular disease, and stroke in the years soon after index date (Figure 1), but the direction of association then changed after 5 years for myocardial infarction and stroke. However, a breast cancer diagnosis was associated with an increased risk of sudden cardiac arrest, arrhythmia, heart failure,

Table 2. Rates, Rate Difference, and Unadjusted and Adjusted HRs for Cardiovascular Risk

Outcome	Breast Cancer		Noncancer		Rate Difference (95% CI) ^b	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^c
	Events/ Follow-Up ^a	Rate (95% CI) ^b	Events/ Follow-Up ^a	Rate (95% CI) ^b			
CAD	12,329/ 345,077	35.73 (35.10 to 36.36)	63,246/ 1,718,418	36.80 (36.52 to 37.09)	-2.27 (-4.19 to 0.34)	0.97 (0.96 to 0.99)	0.96 (0.95 to 0.98)
Angina	8,308/ 351,468	23.64 (23.13 to 24.15)	43,913/ 1,750,535	25.09 (24.85 to 25.32)	-3.52 (-5.07 to -1.97)	0.94 (0.92 to 0.97)	0.93 (0.91 to 0.95)
MI	4,696/ 388,164	12.10 (11.75 to 12.44)	24,307/ 1,938,354	12.54 (12.38 to 12.70)	-0.95 (-2.00 to 0.10)	0.98 (0.95 to 1.00)	0.97 (0.94 to 1.00)
Revascularization	2,533/ 388,302	6.52 (6.27 to 6.78)	14,309/ 1,935,943	7.39 (7.27 to 7.51)	-2.24 (-3.02 to -1.46)	0.89 (0.86 to 0.93)	0.89 (0.85 to 0.92)
SCA	2,659/ 398,161	6.68 (6.42 to 6.93)	12,914/ 1,994,861	6.47 (6.36 to 6.59)	0.72 (-0.04 to 1.49)	1.05 (1.01 to 1.09)	1.05 (1.01 to 1.10)
PVD	13,387/ 334,516	40.02 (39.34 to 40.70)	71,024/ 1,655,613	42.90 (42.58 to 43.21)	-6.89 (-8.97 to -4.81)	0.94 (0.92 to 0.95)	0.93 (0.91 to 0.94)
Stroke	15,387/ 330,234	46.59 (45.86 to 47.33)	76,482/ 1,637,404	46.71 (46.38 to 47.04)	0.75 (-1.49 to 3.00)	0.99 (0.98 to 1.01)	0.98 (0.97 to 1.00)
Arrhythmia	21,502/ 266,307	80.74 (79.66 to 81.82)	107,132/ 1,428,733	74.98 (74.53 to 75.43)	17.26 (13.99 to 20.52)	1.09 (1.07 to 1.10)	1.09 (1.07 to 1.10)
Heart failure	19,238/ 298,766	64.39 (63.48 to 65.30)	90,945/ 1,524,638	59.65 (59.26 to 60.04)	14.49 (11.74 to 17.24)	1.08 (1.07 to 1.10)	1.07 (1.06 to 1.09)
Pericarditis	2,718/ 390,776	6.96 (6.69 to 7.22)	9,758/ 1,969,373	4.95 (4.86 to 5.05)	5.63 (4.86 to 6.41)	1.42 (1.36 to 1.47)	1.43 (1.38 to 1.49)
VHD	20,575/ 263,089	78.21 (77.14 to 79.27)	101,538/ 1,413,310	71.84 (71.40 to 72.29)	18.48 (15.27 to 21.69)	1.09 (1.08 to 1.11)	1.09 (1.07 to 1.11)
VTE	4,141/ 385,863	10.73 (10.40 to 11.06)	13,279/ 1,954,840	6.79 (6.68 to 6.91)	11.03 (10.07 to 11.98)	1.59 (1.54 to 1.64)	1.61 (1.55 to 1.66)
DVT	3,921/ 386,484	10.15 (9.83 to 10.46)	12,061/ 1,958,307	6.16 (6.05 to 6.27)	11.14 (10.21 to 12.07)	1.65 (1.60 to 1.71)	1.67 (1.62 to 1.73)
PE	356/ 398,784	0.89 (0.80 to 0.99)	1,711/ 1,997,803	0.86 (0.82 to 0.90)	0.12 (-0.16 to 0.40)	1.03 (0.93 to 1.15)	0.98 (0.87 to 1.10)

Abbreviations: CAD, coronary artery disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; SCA, sudden cardiac arrest; VHD, valvular heart disease; VTE, venous thromboembolism.

^aPerson-years.

^bPer 1,000 person-years.

^cAdjusted for age, race/ethnicity, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease prior to index date (other than the disease of interest).

pericarditis, valvular heart disease, and DVT in the years soon after index date, which was most pronounced in the first year, but continued to show evidence of an increased risk after 5 years (except sudden cardiac arrest and valvular heart disease). Similar patterns were seen in flexible parametric survival models, in which variation in HRs over time were fitted as a smooth function (Figure 1).

There was also evidence of effect measure modification by race/ethnicity for the composite coronary artery disease and venous thromboembolic outcomes, and for myocardial infarction and DVT (Table 4, supplemental eTable 3). A breast cancer diagnosis was associated with an increased risk of coronary artery disease and myocardial infarction in Black women (adjusted HRs, 1.08; 95% CI, 1.02–1.15, and 1.10; 95% CI, 1.00–1.22, respectively), but a decreased risk of these in

White women (adjusted HRs, 0.95; 95% CI, 0.94–0.97, and 0.96; 95% CI, 0.93–0.99, respectively). A diagnosis of breast cancer was associated with an increased risk of both the composite venous thromboembolism outcome and DVT in all races/ethnicities, but there was a larger increased risk of both outcomes in Black versus White women.

There was evidence of effect measure modification by prior CVD for many of the outcomes (supplemental eTable 4), with higher relative risks among those without a prior cardiovascular diagnosis. There was also evidence of effect measure modification by age for several cardiovascular outcomes (supplemental eTable 5), with higher relative risks among younger groups (other than for stroke).

When those diagnosed with breast cancer were subdivided into stage, grade, and ER/PR status, there was consistently a greater risk of all cardiovascular outcomes in those diagnosed with stage III (vs earlier stage), grade 3

Table 3. Adjusted HRs for Cardiovascular Risk by Time Since Index Date

Outcome	Time Since Index Date	Adjusted HR ^a (95% CI)	P Value for Interaction
CAD	0–1 y	0.92 (0.89–0.96)	.02
	1–3 y	0.97 (0.94–1.00)	
	3–5 y	0.96 (0.92–1.00)	
	≥5 y	1.02 (0.97–1.06)	
Angina	0–1 y	0.87 (0.83–0.91)	<.01
	1–3 y	0.94 (0.90–0.97)	
	3–5 y	0.95 (0.90–1.00)	
	≥5 y	0.99 (0.94–1.05)	
MI	0–1 y	0.96 (0.89–1.04)	<.01
	1–3 y	0.94 (0.89–0.99)	
	3–5 y	0.91 (0.86–0.97)	
	≥5 y	1.09 (1.02–1.16)	
Revascularization	0–1 y	0.74 (0.66–0.82)	<.01
	1–3 y	0.92 (0.86–0.98)	
	3–5 y	0.88 (0.81–0.96)	
	≥5 y	0.98 (0.89–1.07)	
SCA	0–1 y	1.20 (1.09–1.33)	.06
	1–3 y	1.04 (0.97–1.11)	
	3–5 y	1.02 (0.94–1.11)	
	≥5 y	1.02 (0.94–1.11)	
PVD	0–1 y	0.82 (0.79–0.86)	<.01
	1–3 y	0.92 (0.89–0.94)	
	3–5 y	0.96 (0.92–1.00)	
	≥5 y	1.03 (0.99–1.08)	
Stroke	0–1 y	0.94 (0.91–0.98)	<.01
	1–3 y	0.96 (0.94–0.99)	
	3–5 y	1.02 (0.98–1.06)	
	≥5 y	1.05 (1.01–1.09)	
Arrhythmia	0–1 y	1.15 (1.12–1.19)	<.01
	1–3 y	1.05 (1.03–1.08)	
	3–5 y	1.10 (1.07–1.14)	
	≥5 y	1.07 (1.03–1.11)	
Heart failure	0–1 y	1.17 (1.13–1.20)	<.01
	1–3 y	1.03 (1.01–1.06)	
	3–5 y	1.05 (1.01–1.09)	
	≥5 y	1.07 (1.03–1.11)	

(continued)

Table 3. Adjusted HRs for Cardiovascular Risk by Time Since Index Date (cont.)

Outcome	Time Since Index Date	Adjusted HR ^a (95% CI)	P Value for Interaction
Pericarditis	0–1 y	2.10 (1.92–2.30)	.00
	1–3 y	1.32 (1.23–1.41)	
	3–5 y	1.39 (1.28–1.52)	
	≥5 y	1.23 (1.13–1.35)	
VHD	0–1 y	1.28 (1.24–1.32)	<.01
	1–3 y	1.05 (1.02–1.07)	
	3–5 y	1.01 (0.98–1.05)	
	≥5 y	1.02 (0.98–1.06)	
VTE	0–1 y	2.24 (2.08–2.40)	<.01
	1–3 y	1.52 (1.44–1.61)	
	3–5 y	1.52 (1.41–1.63)	
	≥5 y	1.35 (1.25–1.46)	
DVT	0–1 y	2.39 (2.22–2.57)	<.01
	1–3 y	1.56 (1.48–1.66)	
	3–5 y	1.60 (1.48–1.72)	
	≥5 y	1.39 (1.28–1.50)	
PE	0–1 y	1.05 (0.80–1.38)	.74
	1–3 y	1.03 (0.85–1.26)	
	3–5 y	0.89 (0.71–1.12)	
	≥5 y	0.95 (0.75–1.19)	

Abbreviations: CAD, coronary artery disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; SCA, sudden cardiac arrest; VHD, valvular heart disease; VTE, venous thromboembolism.

^aAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease prior to index date (other than the disease of interest).

comparison cohort, evidence was seen of an increased risk of incident sudden cardiac arrest, arrhythmia, heart failure, pericarditis, valvular heart disease, and DVT during follow-up among those diagnosed with breast cancer compared with their matched noncancer comparisons, despite little difference between the groups in the prevalence of preexisting CVD at baseline. Although these effects were most pronounced in the first year, risks remained elevated for arrhythmia, heart failure, pericarditis, and DVT after 5 years. There was evidence of a decreased risk of incident angina, myocardial infarction, revascularization, peripheral vascular disease, and stroke in breast cancer survivors, but this was not constant over time. The cardiovascular risk during follow-up was consistently higher in Black women diagnosed with breast cancer compared with White women, regardless of whether there was an overall increased or decreased risk of outcomes over all of follow-up, which is consistent with racial differences in overall cardiovascular risk in the United States.¹⁸ Finally, there was consistently a greater risk of all cardiovascular outcomes in those diagnosed with stage III, grade 3, and ER/PR-negative breast cancer, which is likely a reflection of the more aggressive cancer treatment regimens used in these subtypes.

(vs lower grade), and ER/PR-negative (vs ER/PR-positive) breast cancer compared with their noncancer comparisons (supplemental eTables 6–8).

Sensitivity Analyses

There were small differences in the effect estimates for all cardiovascular outcomes when comparing the results for the primary analyses and analyses using only inpatient claims (supplemental eTable 9), but differences did not materially change conclusions.

Discussion

In this large US cancer registry-based study of women aged >65 years with breast cancer versus a noncancer

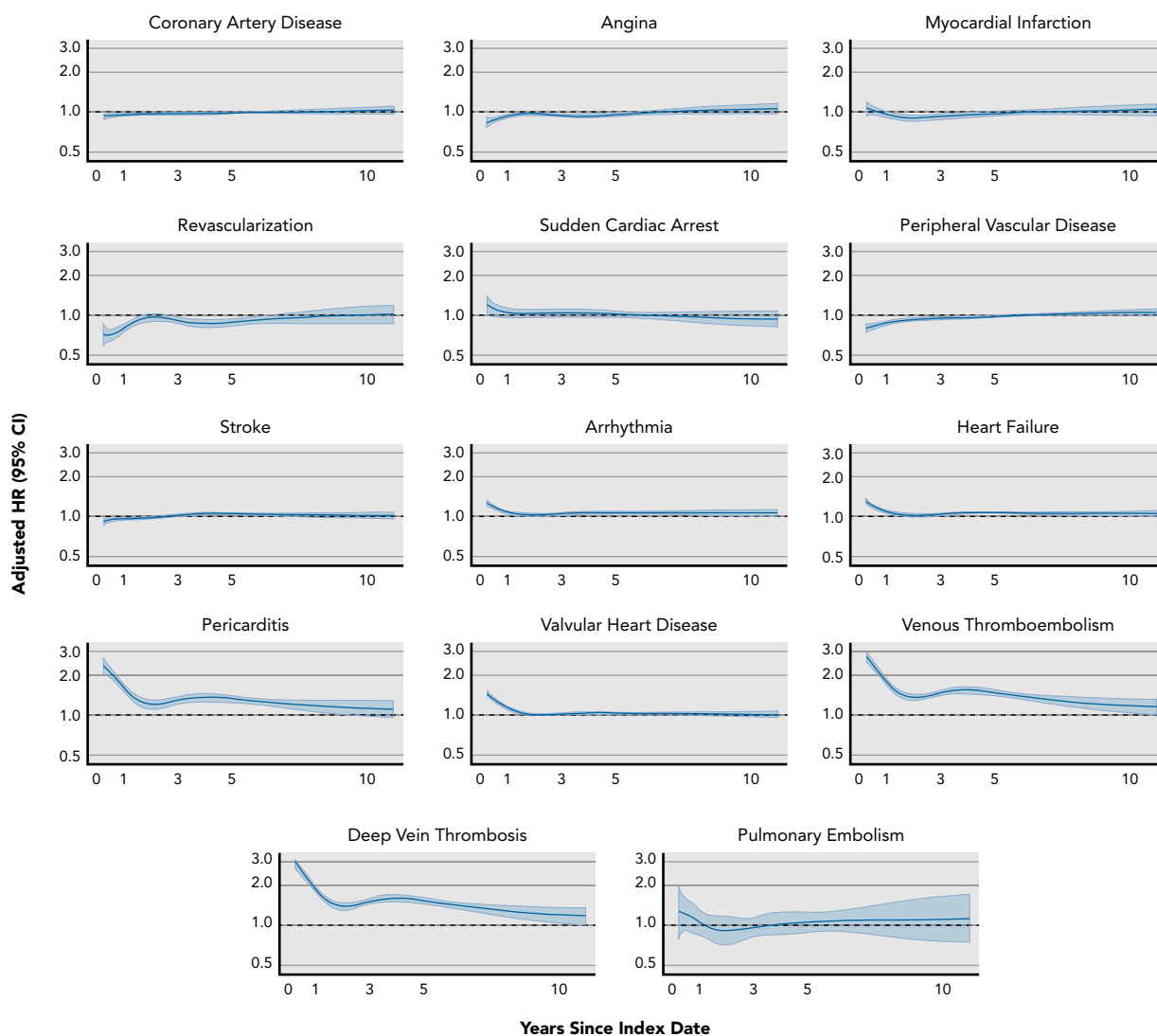


Figure 1. Flexible parametric models for the association between breast cancer and a range of cardiovascular outcomes over time since index date. Abbreviation: HR, hazard ratio.

Comparison With Other Studies

Several studies have suggested an increased risk of heart failure in older women with a breast cancer diagnosis (relative risks ranged from 0.98–1.35),^{4–6,13} which is similar to our result over the whole time period (adjusted HR, 1.07; 95% CI, 1.06–1.09). However, we additionally suggest that this effect is sustained after 5 years, which has also been shown in Canadian and UK populations.^{4,13} Furthermore, although studies have reported both an increased and a decreased risk of stroke in breast cancer survivors,^{4–6,13} none have suggested that the risk of stroke in those diagnosed with breast cancer compared with noncancer comparisons changes as time after breast cancer diagnosis increases, with a decreased risk in the time shortly after breast cancer, followed by an increased

risk after 5 years, as we have shown. Our results dissect the previous evidence for valvular heart disease, with one study reporting a larger estimated effect and another reporting no association.^{6,13} Previous studies estimating risk of coronary artery disease in individuals with a breast cancer diagnosis have reported conflicting results, and generally had little precision to detect any effects.^{4–6,9} However, a recent study in the United Kingdom reported a decreased risk of coronary artery disease in women with breast cancer compared with cancer-free comparisons (HR, 0.84; 95% CI, 0.77–0.92),¹³ which is similar, but more protective, compared with results estimated in this population in the United States (HR, 0.96; 95% CI, 0.95–0.98). Several studies have reported an increased risk of venous thromboembolism in women with a breast cancer

diagnosis compared with those without,^{8,10,13} with 2 reporting a similar sustained increased risk after 5 years.

Potential Reasons for Differences in Cardiovascular Risk

It is likely that those diagnosed with breast cancer have a higher body mass index, are more likely to smoke,¹⁹ consume more alcohol,²⁰ have a sedentary lifestyle,²¹ and have metabolic syndrome,²² which are all known to increase cardiovascular risk.^{23–27} The results showing an increased risk of outcome in those with a breast cancer diagnosis could therefore be partly explained by differences in modifiable risk factors, but this will not explain any apparent reduced cardiovascular risk associated with a breast cancer diagnosis.

Effects of cancer treatments could also contribute to the differences in cardiovascular risk. For example, all doses of the anthracyclines doxorubicin and epirubicin are known to increase risk of heart failure, arrhythmias, atrial fibrillation, and left ventricular dysfunction^{28–30}; there is also a known association between trastuzumab and heart failure.³¹ Myocardial infarction and arrhythmias are reported as side effects of 5-fluorouracil,^{32–34} but any effects are thought to be acute, with long-term cardiotoxicity uncommon.³⁵ It has been suggested that users of the hormone therapy tamoxifen are at an increased risk of venous thromboembolism compared with aromatase inhibitor users, but at a decreased risk of other cardiovascular outcomes, such as coronary heart disease.^{36–38} The increased risk of venous thromboembolism in tamoxifen users is likely a key driver for the increased risk of DVT seen in patients with breast cancer compared with the noncancer comparison cohort, and the decreasing risk over time suggests that this adverse effect is likely to occur early in treatment. A reduced risk of coronary artery diseases in tamoxifen users may also explain the low risk of such outcomes soon after breast cancer diagnosis that returns to neutral after 5 years, driven by women who undergo treatment regimens in which tamoxifen is stopped after 5 years, and hence any protective effect is removed. The increasing risk of coronary artery diseases over time may also be partially attributed to the dose-dependent linear increase in risk for major coronary events due to exposure to ionizing radiation.³⁹ Finally, cardiovascular events do not occur independently and may influence each other. For example, arrhythmias may be due to symptomatic heart failure or ischemia and may contribute to embolic stroke over time.

Although information on administered or dispensed breast cancer treatments is available in claims data, we did not adjust for these in our analysis. This is because the aim of the analysis was to describe the incidence of a range of cardiovascular diseases in women with breast

Table 4. Adjusted HRs for Risk of CAD, MI, VTE, and DVT, Stratified by Race/Ethnicity

Outcome	Race/Ethnicity	Adjusted HR ^a (95% CI)	P Value for Interaction
CAD	White	0.95 (0.94–0.97)	<.01
	Black	1.08 (1.02–1.15)	
	Other	0.94 (0.81–1.10)	
	Asian	1.00 (0.88–1.14)	
	Hispanic	0.90 (0.76–1.06)	
	Native American	1.12 (0.74–1.69)	
MI	White	0.96 (0.93–0.99)	.04
	Black	1.10 (1.00–1.22)	
	Other	1.04 (0.81–1.33)	
	Asian	1.08 (0.87–1.33)	
	Hispanic	0.78 (0.58–1.05)	
	Native American	1.44 (0.66–3.11)	
VTE	White	1.58 (1.52–1.64)	.02
	Black	1.83 (1.65–2.04)	
	Other	2.41 (1.71–3.39)	
	Asian	1.49 (1.09–2.05)	
	Hispanic	1.53 (1.05–2.24)	
	Native American	2.15 (0.83–5.57)	
DVT	White	1.65 (1.59–1.71)	.03
	Black	1.84 (1.65–2.05)	
	Other	2.84 (1.96–4.10)	
	Asian	1.54 (1.09–2.18)	
	Hispanic	1.62 (1.11–2.36)	
	Native American	2.16 (0.84–5.56)	

Abbreviations: CAD, coronary artery disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; VTE, venous thromboembolism.

^aAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease prior to index date (other than the disease of interest).

cancer compared with similar women without cancer based on their characteristics at start of follow-up, rather than make inference about the causal reasons behind any difference in cardiovascular risk between these women. However, results from this study will inform further causal exploration of the treatments and risk factors that alter the risk of specific CVDs in women with breast cancer.

Finally, it is possible that the lower prevalence of CVDs prior to start of follow-up in those diagnosed with breast cancer may be the result of unmeasured confounding by socioeconomic status, given the known increased risk of breast cancer incidence in women with a higher socioeconomic status.⁴⁰ The difference could also be due to differential ascertainment of CVD prior to start of follow-up; that is, leading up to breast cancer diagnosis, healthcare may be focused on the cancer, but once a cancer treatment plan is set, other conditions may come into focus and be retrospectively diagnosed (eg, patient may resume care with primary care and cardiology). This differential ascertainment of CVDs may also explain the increase in valvular heart disease shortly after breast cancer diagnosis, because there is no clear biologic rationale for such an effect. However,

further study is needed to understand completely the reasons for differences in CVD prior to and soon after the start of follow-up.

Strengths and Limitations

SEER-Medicare includes a large, diverse population of older women diagnosed with breast cancer, along with a matched noncancer comparison cohort, and therefore results are likely to be generalizable to women aged >65 years diagnosed with breast cancer in both the United States and other developed countries.

A limitation of using this database is that modifiable risk factors for both breast cancer and CVD, such as body mass index, smoking, alcohol, a sedentary lifestyle, and hyperlipidemia, are either not captured or poorly captured in SEER-Medicare.^{41,42} However, the aim of these analyses was to assess the overall cardiovascular burden in patients with breast cancer versus those without cancer, and not an attempt to infer any causal relationship between a breast cancer diagnosis and cardiovascular morbidity. Furthermore, data on HER2 status were not available because collection was not required until 2010 in SEER, and therefore there was a high degree of incompleteness. Finally, diagnoses of breast cancer, CVDs, and other measured clinical conditions relied on correct specification of ICD-10 codes, and as with any coding system, codes may be inconsistently or incorrectly used.

Conclusions

There is evidence of increased risks of several cardiovascular outcomes in older women diagnosed with breast cancer in the United States compared with similar women without cancer, with increased risks of arrhythmia, heart failure, pericarditis, and DVT persisting several years after diagnosis. Our results highlight the importance of periodic cardiovascular evaluation of women diagnosed with breast cancer to ensure adequate management of cardiovascular risk.

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Risk of Cardiovascular Diseases Among Older Breast Cancer Survivors in the United States: A Matched Cohort Study

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eTable 1: ICD-9 and CPT/HCPCS Codes Used to Identify Cardiovascular Disease Outcomes of Interest

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eTable 9: Rates, Rate Difference, and HRs for Cardiovascular Risk, Using Only Inpatient Claims to Identify Cardiovascular Outcomes

eTable 1. ICD-9 and CPT/HCPCS Codes Used to Identify Cardiovascular Disease Outcomes of Interest

Outcomes	ICD-9 Diagnosis and Procedure Codes	CPT/HCPCS Codes
Angina	411.1, 413.1, 413.9	
Myocardial infarction	410.11, 410.01, 410.31, 410.21, 410.41, 410.81, 410.51, 410.61, 410.91, 410.71	
Revascularization procedures	36.0×, 36.1×, 36.2, 36.3	33140, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33533, 33534, 33535, 33536, 92920, 92924, 92928, 92933, 92937, 92941, 92943, 92980, 92981, 92982, 92984, 92995, 92996, 92997, 92998
Sudden cardiac arrest	427.5	
Stroke (hemorrhagic and ischemic)	430.×, 431.×, 432.1, 432.0, 432.9, 433.91, 433.21, 433.01, 433.11, 433.31, 433.81, 434.01, 434.×, 435.0, 435.1, 435.3, 435.8, 435.9, 436.×	
Arrhythmia	427.31, 427.32, 427.41, 427.42, 427.61, 427.0, 427.69, 427.60, 427.81, 427.89, 427.9	
Deep venous thromboembolism	415.1×	
Pulmonary embolism	415.0, 415.12, 415.13, 415.19	
Heart failure	428.1, 428.0, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9, 414.8, 425.4, 425.11, 425.18, 425.0, 425.3, 425.5, 425.9, 425.2, 425.8	
Pericarditis	420.91, 420.90, 420.99, 423.1, 423.2, 423.0, 423.9, 423.3, 423.8, 420.0	
Valvular heart disease	394.0, 394.1, 394.2, 394.9, 395.0, 395.1, 395.2, 395.9, 397.0, 396.0, 396.1, 396.2, 396.3, 397.9, 396.8, 396.9, 424.0, 424.1, 424.2, 424.3	
Peripheral vascular disease	443.89, 443.9	

eTable 2. Adjusted HRs for Cardiovascular Risk, Stratified by Time Since Index Date, Including Time Up Until 90 Days After Index

Outcome	Time Since Index Date	Events, n		Adjusted HR (95% CI) ^a	P Value for Interaction
		Breast Cancer	Noncancer		
Coronary artery disease	0–30 d	634	1,663	1.95 (1.75–2.18)	<.01
	30–90 d	1,043	3,383	1.51 (1.40–1.63)	
	90 d to 1 y	2,498	13,091	0.93 (0.90–0.97)	
	1–3 y	4,710	23,931	0.97 (0.94–0.99)	
	3–5 y	2,649	13,872	0.96 (0.92–1.00)	
	≥5 y	2,472	12,352	1.02 (0.97–1.06)	
Angina	0–30 d	503	1,251	2.08 (1.84–2.35)	<.01
	30–90 d	808	2,561	1.54 (1.41–1.68)	
	90 d to 1 y	1,754	9,872	0.88 (0.83–0.92)	
	1–3 y	3,307	17,147	0.94 (0.90–0.97)	
	3–5 y	1,761	9,276	0.95 (0.90–1.00)	
	≥5 y	1,486	7,618	0.99 (0.94–1.05)	
Myocardial infarction	0–30 d	155	452	1.81 (1.46–2.25)	<.01
	30–90 d	242	941	1.28 (1.10–1.50)	
	90 d to 1 y	782	3,845	0.96 (0.90–1.04)	
	1–3 y	1,593	8,350	0.94 (0.89–0.99)	
	3–5 y	1,056	5,844	0.91 (0.86–0.97)	
	≥5 y	1,265	6,268	1.09 (1.02–1.16)	
Revascularization	0–30 d	78	328	1.33 (1.01–1.76)	<.01
	30–90 d	196	652	1.58 (1.34–1.88)	
	90 d to 1 y	404	2,678	0.74 (0.67–0.81)	
	1–3 y	1,010	5,411	0.92 (0.86–0.98)	
	3–5 y	587	3,308	0.88 (0.81–0.96)	
	≥5 y	532	2,912	0.98 (0.89–1.07)	
Sudden cardiac arrest	0–30 d	40	209	1.00 (0.68–1.46)	.01
	30–90 d	129	444	1.42 (1.15–1.76)	
	90 d to 1 y	428	1,853	1.19 (1.08–1.32)	
	1–3 y	912	4,322	1.04 (0.97–1.11)	
	3–5 y	632	3,156	1.02 (0.94–1.11)	
	≥5 y	687	3,583	1.02 (0.94–1.11)	
Peripheral vascular disease	0–30 d	540	1,792	1.38 (1.24–1.54)	<.01
	30–90 d	994	3,615	1.39 (1.29–1.50)	
	90 d to 1 y	2,392	14,194	0.82 (0.79–0.86)	
	1–3 y	5,033	26,506	0.91 (0.89–0.94)	
	3–5 y	3,049	15,701	0.96 (0.92–1.00)	
	≥5 y	2,913	14,623	1.03 (0.99–1.08)	
Stroke	0–30 d	639	1,979	1.63 (1.47–1.81)	<.01
	30–90 d	980	4,083	1.16 (1.08–1.25)	
	90 d to 1 y	2,972	15,356	0.94 (0.91–0.98)	
	1–3 y	5,806	29,031	0.96 (0.94–0.99)	
	3–5 y	3,521	16,770	1.02 (0.98–1.06)	
	≥5 y	3,088	15,325	1.05 (1.01–1.09)	
Arrhythmia	0–30 d	2,511	3,040	4.53 (4.21–4.86)	<.01
	30–90 d	3,867	6,082	3.35 (3.19–3.52)	
	90 d to 1 y	4,982	22,892	1.16 (1.12–1.19)	
	1–3 y	8,185	41,287	1.05 (1.03–1.08)	
	3–5 y	4,500	22,800	1.11 (1.07–1.14)	
	≥5 y	3,835	20,153	1.07 (1.03–1.11)	
Heart failure	0–30 d	1,190	2,572	2.28 (2.10–2.49)	<.01
	30–90 d	2,264	5,040	2.28 (2.15–2.41)	
	90 d to 1 y	4,479	19,199	1.17 (1.13–1.21)	
	1–3 y	6,962	33,672	1.03 (1.01–1.06)	
	3–5 y	4,058	19,678	1.05 (1.01–1.09)	
	≥5 y	3,739	18,396	1.07 (1.03–1.11)	

(continued on next page)

eTable 2. Adjusted HRs for Cardiovascular Risk, Stratified by Time Since Index Date, Including Time Up Until 90 Days After Index (cont.)

Outcome	Time Since Index Date	Events, n		Adjusted HR (95% CI) ^a	P Value for Interaction
		Breast Cancer	Noncancer		
Pericarditis	0–30 d	101	148	2.93 (2.17–3.97)	<.01
	30–90 d	280	375	3.97 (3.29–4.78)	
	90 d to 1 y	625	1,533	2.11 (1.93–2.31)	
	1–3 y	886	3,395	1.32 (1.23–1.42)	
	3–5 y	614	2,278	1.39 (1.28–1.52)	
	≥5 y	593	2,552	1.23 (1.13–1.35)	
Valvular heart disease	0–30 d	2,122	3,281	3.36 (3.13–3.61)	<.01
	30–90 d	4,457	6,063	4.08 (3.89–4.28)	
	90 d to 1 y	5,447	22,832	1.28 (1.25–1.32)	
	1–3 y	7,745	39,521	1.05 (1.02–1.07)	
	3–5 y	4,008	21,151	1.01 (0.98–1.05)	
	≥5 y	3,375	18,034	1.02 (0.98–1.06)	
Venous thromboembolism	0–30 d	128	275	2.54 (1.97–3.28)	<.01
	30–90 d	311	501	3.11 (2.66–3.63)	
	90 d to 1 y	1,018	2,269	2.25 (2.09–2.41)	
	1–3 y	1,409	4,711	1.52 (1.44–1.61)	
	3–5 y	895	3,088	1.52 (1.41–1.63)	
	≥5 y	819	3,211	1.35 (1.25–1.46)	
Deep vein thrombosis	0–30 d	125	243	2.80 (2.15–3.65)	<.01
	30–90 d	302	455	3.27 (2.79–3.84)	
	90 d to 1 y	981	2,055	2.39 (2.22–2.57)	
	1–3 y	1,334	4,326	1.56 (1.48–1.66)	
	3–5 y	839	2,750	1.60 (1.48–1.72)	
	≥5 y	767	2,930	1.39 (1.28–1.50)	
Pulmonary embolism	0–30 d	4	42	0.63 (0.25–1.61)	.56
	30–90 d	16	62	1.40 (0.79–2.48)	
	90 d to 1 y	63	286	1.09 (0.83–1.43)	
	1–3 y	115	560	1.04 (0.85–1.27)	
	3–5 y	87	453	0.89 (0.71–1.12)	
	≥5 y	91	412	0.95 (0.75–1.20)	

Abbreviation: HR, hazard ratio.

^aAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease (other than the disease of interest).

eTable 3. Adjusted HRs for Cardiovascular Risk, Stratified by Race/Ethnicity

Outcome	Race/Ethnicity	Adjusted HR (95% CI) ^a	P Value for Interaction
CAD	White	0.95 (0.94–0.97)	<.01
	Black	1.08 (1.02–1.15)	
	Other	0.94 (0.81–1.10)	
	Asian	1.00 (0.88–1.14)	
	Hispanic	0.90 (0.76–1.06)	
	Native American	1.12 (0.74–1.69)	
Angina	White	0.93 (0.90–0.95)	.62
	Black	0.99 (0.92–1.07)	
	Other	0.93 (0.77–1.12)	
	Asian	0.92 (0.79–1.08)	
	Hispanic	0.96 (0.80–1.15)	
	Native American	1.15 (0.70–1.88)	
MI	White	0.96 (0.93–0.99)	.04
	Black	1.10 (1.00–1.22)	
	Other	1.04 (0.81–1.33)	
	Asian	1.08 (0.87–1.33)	
	Hispanic	0.78 (0.58–1.05)	
	Native American	1.44 (0.66–3.11)	
Revascularization	White	0.88 (0.85–0.92)	.55
	Black	0.94 (0.81–1.09)	
	Other	0.98 (0.67–1.41)	
	Asian	0.89 (0.65–1.23)	
	Hispanic	0.78 (0.54–1.14)	
	Native American	1.60 (0.78–3.27)	
SCA	White	1.03 (0.99–1.08)	.14
	Black	1.20 (1.07–1.33)	
	Other	0.89 (0.64–1.22)	
	Asian	1.12 (0.85–1.47)	
	Hispanic	1.07 (0.76–1.50)	
	Native American	1.70 (0.61–4.73)	
PVD	White	0.93 (0.91–0.94)	.90
	Black	0.93 (0.87–0.99)	
	Other	1.00 (0.86–1.17)	
	Asian	0.89 (0.78–1.02)	
	Hispanic	0.91 (0.77–1.07)	
	Native American	0.84 (0.54–1.31)	
Stroke	White	0.98 (0.96–1.00)	.08
	Black	1.01 (0.95–1.07)	
	Other	0.98 (0.86–1.12)	
	Asian	1.00 (0.89–1.13)	
	Hispanic	1.24 (1.06–1.45)	
	Native American	0.96 (0.66–1.42)	
Arrhythmia	White	1.08 (1.07–1.10)	.14
	Black	1.09 (1.04–1.15)	
	Other	1.09 (0.97–1.22)	
	Asian	1.20 (1.08–1.33)	
	Hispanic	1.15 (1.00–1.32)	
	Native American	0.74 (0.51–1.07)	

(continued)

eTable 3. Adjusted HRs for Cardiovascular Risk, Stratified by Race/Ethnicity (cont.)

Outcome	Race/Ethnicity	Adjusted HR (95% CI) ^a	P Value for Interaction
Heart failure	White	1.07 (1.05–1.09)	.35
	Black	1.09 (1.03–1.15)	
	Other	1.05 (0.92–1.20)	
	Asian	1.08 (0.97–1.20)	
	Hispanic	1.27 (1.09–1.47)	
	Native American	1.24 (0.82–1.87)	
Pericarditis	White	1.42 (1.36–1.49)	.46
	Black	1.48 (1.30–1.69)	
	Other	1.43 (0.96–2.15)	
	Asian	1.71 (1.27–2.30)	
	Hispanic	1.50 (1.00–2.26)	
	Native American	0.37 (0.08–1.74)	
VHD	White	1.08 (1.07–1.10)	.39
	Black	1.12 (1.06–1.18)	
	Other	1.23 (1.09–1.38)	
	Asian	1.10 (0.99–1.22)	
	Hispanic	1.09 (0.94–1.27)	
	Native American	1.09 (0.78–1.53)	
VTE	White	1.58 (1.52–1.64)	.02
	Black	1.83 (1.65–2.04)	
	Other	2.41 (1.71–3.39)	
	Asian	1.49 (1.09–2.05)	
	Hispanic	1.53 (1.05–2.24)	
	Native American	2.15 (0.83–5.57)	
DVT	White	1.65 (1.59–1.71)	.03
	Black	1.84 (1.65–2.05)	
	Other	2.84 (1.96–4.10)	
	Asian	1.54 (1.09–2.18)	
	Hispanic	1.62 (1.11–2.36)	
	Native American	2.16 (0.84–5.56)	
PE	White	0.95 (0.84–1.07)	.15
	Black	1.32 (0.91–1.93)	
	Other	0.37 (0.10–1.34)	
	Asian	1.56 (0.79–3.06)	
	Hispanic	1.48 (0.21–10.50)	
	Native American	0.95 (0.84–1.07)	

Abbreviations: CAD, coronary artery disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; SCA, sudden cardiac arrest; VHD, valvular heart disease; VTE, venous thromboembolism.

^aAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease (other than the disease of interest).

eTable 4. Adjusted HRs for Cardiovascular Risk, Stratified by Cardiovascular Disease Before Diagnosis

Outcome	CVD Before Diagnosis	Adjusted HR (95% CI) ^a	P Value for Interaction
CAD	No	0.98 (0.96–1.01)	.05
	Yes	0.94 (0.91–0.97)	
Angina	No	0.94 (0.91–0.97)	.45
	Yes	0.92 (0.89–0.96)	
MI	No	1.00 (0.96–1.04)	.05
	Yes	0.94 (0.89–0.98)	
Revascularization	No	0.88 (0.83–0.93)	.66
	Yes	0.90 (0.84–0.96)	
SCA	No	1.12 (1.05–1.18)	.01
	Yes	0.99 (0.93–1.05)	
PVD	No	0.95 (0.92–0.97)	.01
	Yes	0.89 (0.87–0.92)	
Stroke	No	1.00 (0.98–1.02)	.02
	Yes	0.96 (0.93–0.98)	
Arrhythmia	No	1.11 (1.09–1.13)	<.01
	Yes	1.04 (1.01–1.07)	
Heart failure	No	1.11 (1.09–1.14)	<.01
	Yes	0.99 (0.96–1.02)	
Pericarditis	No	1.59 (1.50–1.68)	<.01
	Yes	1.25 (1.18–1.34)	
VHD	No	1.11 (1.09–1.13)	<.01
	Yes	1.04 (1.01–1.07)	
VTE	No	1.79 (1.71–1.87)	<.01
	Yes	1.37 (1.30–1.45)	
DVT	No	1.85 (1.76–1.94)	<.01
	Yes	1.44 (1.36–1.53)	
PE	No	1.10 (0.93–1.30)	.07
	Yes	0.88 (0.74–1.03)	

Abbreviations: CAD, coronary artery disease; CVD, cardiovascular disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; SCA, sudden cardiac arrest; VHD, valvular heart disease; VTE, venous thromboembolism.
^aAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other CVD (other than the disease of interest).

eTable 5. Adjusted HRs for Cardiovascular Risk, Stratified by Current Age

Outcome	Current Age, y	Adjusted HR (95% CI) ^a	P Value for Interaction
CAD	66–75	0.95 (0.92–0.98)	.44
	>75–85	0.97 (0.94–0.99)	
	>85	0.98 (0.94–1.02)	
Angina	66–75	0.88 (0.84–0.91)	<.01
	>75–85	0.94 (0.91–0.97)	
	>85	1.02 (0.97–1.07)	
MI	66–75	1.01 (0.95–1.08)	.28
	>75–85	0.95 (0.91–0.99)	
	>85	0.98 (0.93–1.03)	
Revascularization	66–75	0.81 (0.75–0.87)	.01
	>75–85	0.92 (0.87–0.97)	
	>85	0.96 (0.87–1.07)	
SCA	66–75	1.23 (1.13–1.34)	<.01
	>75–85	1.05 (1.00–1.12)	
	>85	0.95 (0.88–1.02)	
PVD	66–75	0.91 (0.88–0.95)	.53
	>75–85	0.93 (0.90–0.95)	
	>85	0.94 (0.91–0.97)	
Stroke	66–75	1.01 (0.97–1.04)	.06
	>75–85	0.99 (0.97–1.01)	
	>85	0.95 (0.92–0.98)	
Arrhythmia	66–75	1.15 (1.12–1.18)	<.01
	>75–85	1.07 (1.05–1.09)	
	>85	1.04 (1.00–1.07)	
Heart failure	66–75	1.24 (1.21–1.28)	<.01
	>75–85	1.02 (1.00–1.04)	
	>85	1.01 (0.98–1.04)	
Pericarditis	66–75	1.80 (1.67–1.93)	<.01
	>75–85	1.37 (1.29–1.45)	
	>85	1.18 (1.08–1.30)	
VHD	66–75	1.23 (1.20–1.27)	<.01
	>75–85	1.03 (1.01–1.06)	
	>85	1.01 (0.98–1.05)	
VTE	66–75	2.12 (2.00–2.25)	<.01
	>75–85	1.48 (1.41–1.56)	
	>85	1.36 (1.26–1.46)	
DVT	66–75	2.23 (2.10–2.37)	<.01
	>75–85	1.54 (1.47–1.62)	
	>85	1.40 (1.30–1.51)	
PE	66–75	1.10 (0.89–1.37)	.42
	>75–85	0.92 (0.79–1.08)	
	>85	0.98 (0.77–1.24)	

Abbreviations: CAD, coronary artery disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; SCA, sudden cardiac arrest; VHD, valvular heart disease; VTE, venous thromboembolism.
^aAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease (other than the disease of interest).

eTable 6. HRs for Cardiovascular Risk, Stratified by Cancer Stage

Outcome	Cancer Stage	Unadjusted HR (95% CI)	Adjusted HR ^a (95% CI)
CAD	I	0.91 (0.89–0.93)	0.90 (0.88–0.92)
	II	1.02 (0.99–1.06)	1.00 (0.97–1.04)
	III	1.22 (1.16–1.29)	1.23 (1.16–1.30)
Angina	I	0.94 (0.91–0.96)	0.93 (0.90–0.96)
	II	0.94 (0.90–0.98)	0.92 (0.89–0.96)
	III	1.01 (0.95–1.09)	1.01 (0.94–1.09)
MI	I	0.87 (0.84–0.91)	0.87 (0.84–0.91)
	II	1.06 (1.00–1.11)	1.03 (0.98–1.09)
	III	1.34 (1.23–1.45)	1.35 (1.24–1.48)
Revascularization	I	0.90 (0.85–0.94)	0.90 (0.85–0.94)
	II	0.89 (0.83–0.95)	0.88 (0.82–0.94)
	III	0.88 (0.78–1.01)	0.88 (0.77–1.00)
SCA	I	0.85 (0.80–0.90)	0.84 (0.80–0.89)
	II	1.20 (1.13–1.28)	1.20 (1.12–1.28)
	III	1.74 (1.57–1.93)	1.85 (1.66–2.05)
PVD	I	0.92 (0.90–0.94)	0.91 (0.89–0.93)
	II	0.95 (0.92–0.98)	0.93 (0.90–0.96)
	III	1.03 (0.98–1.09)	1.04 (0.98–1.10)
Stroke	I	0.94 (0.92–0.97)	0.94 (0.92–0.96)
	II	1.03 (1.00–1.06)	1.02 (0.99–1.05)
	III	1.17 (1.12–1.24)	1.17 (1.11–1.23)
Arrhythmia	I	1.03 (1.01–1.05)	1.03 (1.01–1.05)
	II	1.13 (1.10–1.16)	1.13 (1.10–1.15)
	III	1.34 (1.28–1.40)	1.35 (1.29–1.42)
Heart failure	I	0.97 (0.95–0.99)	0.95 (0.93–0.97)
	II	1.18 (1.15–1.21)	1.18 (1.14–1.21)
	III	1.53 (1.46–1.60)	1.56 (1.49–1.64)
Pericarditis	I	1.21 (1.14–1.28)	1.21 (1.15–1.28)
	II	1.52 (1.42–1.62)	1.54 (1.44–1.65)
	III	2.47 (2.22–2.76)	2.59 (2.31–2.90)
VHD	I	1.03 (1.01–1.05)	1.02 (1.00–1.04)
	II	1.14 (1.11–1.17)	1.14 (1.11–1.17)
	III	1.38 (1.31–1.44)	1.38 (1.32–1.45)
VTE	I	1.36 (1.30–1.43)	1.37 (1.31–1.43)
	II	1.70 (1.61–1.80)	1.73 (1.63–1.83)
	III	2.67 (2.44–2.92)	2.79 (2.54–3.07)
DVT	I	1.40 (1.33–1.46)	1.41 (1.34–1.48)
	II	1.79 (1.70–1.90)	1.82 (1.72–1.93)
	III	2.80 (2.55–3.08)	2.92 (2.65–3.22)
PE	I	1.08 (0.95–1.24)	1.00 (0.87–1.16)
	II	0.86 (0.70–1.05)	0.82 (0.66–1.02)
	III	1.37 (1.00–1.89)	1.37 (0.97–1.92)

Abbreviations: CAD, coronary artery disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; SCA, sudden cardiac arrest; VHD, valvular heart disease; VTE, venous thromboembolism.

^aAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease (other than the disease of interest).

eTable 7. HRs for Cardiovascular Risk, Stratified by Grade

Outcome	Grade	Unadjusted HR (95% CI)	Adjusted HR ^a (95% CI)
CAD	1	0.91 (0.88–0.94)	0.90 (0.87–0.94)
	2	0.96 (0.93–0.98)	0.95 (0.92–0.97)
	3	1.07 (1.03–1.11)	1.05 (1.01–1.09)
Angina	1	0.91 (0.87–0.95)	0.91 (0.87–0.95)
	2	0.93 (0.90–0.96)	0.92 (0.89–0.95)
	3	1.00 (0.95–1.04)	0.98 (0.94–1.02)
MI	1	0.88 (0.83–0.93)	0.89 (0.83–0.94)
	2	0.96 (0.92–1.01)	0.96 (0.91–1.00)
	3	1.10 (1.04–1.16)	1.09 (1.02–1.15)
Revascularization	1	0.91 (0.84–0.99)	0.92 (0.85–1.00)
	2	0.85 (0.80–0.90)	0.84 (0.79–0.89)
	3	0.98 (0.91–1.06)	0.96 (0.89–1.03)
SCA	1	0.91 (0.83–0.99)	0.92 (0.84–1.00)
	2	1.03 (0.97–1.09)	1.02 (0.96–1.09)
	3	1.26 (1.17–1.35)	1.26 (1.17–1.35)
PVD	1	0.91 (0.88–0.94)	0.91 (0.88–0.94)
	2	0.93 (0.91–0.96)	0.92 (0.90–0.95)
	3	0.97 (0.93–1.00)	0.94 (0.91–0.97)
Stroke	1	0.99 (0.96–1.02)	0.98 (0.95–1.02)
	2	0.97 (0.94–0.99)	0.96 (0.94–0.98)
	3	1.04 (1.01–1.08)	1.03 (0.99–1.06)
Arrhythmia	1	1.06 (1.03–1.09)	1.06 (1.03–1.09)
	2	1.06 (1.04–1.08)	1.06 (1.04–1.08)
	3	1.16 (1.13–1.20)	1.15 (1.12–1.19)
Heart failure	1	0.96 (0.93–0.99)	0.94 (0.91–0.97)
	2	1.05 (1.03–1.07)	1.04 (1.02–1.07)
	3	1.27 (1.23–1.31)	1.25 (1.22–1.29)
Pericarditis	1	1.18 (1.08–1.28)	1.20 (1.10–1.31)
	2	1.32 (1.25–1.41)	1.34 (1.26–1.42)
	3	1.81 (1.68–1.95)	1.84 (1.70–1.98)
VHD	1	1.00 (0.97–1.03)	1.00 (0.97–1.03)
	2	1.08 (1.05–1.10)	1.07 (1.05–1.10)
	3	1.24 (1.21–1.28)	1.23 (1.20–1.27)
VTE	1	1.29 (1.21–1.39)	1.30 (1.21–1.40)
	2	1.54 (1.47–1.62)	1.57 (1.49–1.65)
	3	1.94 (1.82–2.06)	1.95 (1.84–2.08)
DVT	1	1.33 (1.24–1.43)	1.35 (1.25–1.45)
	2	1.59 (1.51–1.67)	1.62 (1.54–1.71)
	3	2.05 (1.92–2.18)	2.07 (1.94–2.20)
PE	1	0.94 (0.75–1.18)	0.88 (0.70–1.11)
	2	1.14 (0.97–1.32)	1.10 (0.94–1.30)
	3	1.00 (0.80–1.24)	0.91 (0.72–1.16)

Abbreviations: CAD, coronary artery disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; SCA, sudden cardiac arrest; VHD, valvular heart disease; VTE, venous thromboembolism.

^aAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease (other than the disease of interest).

eTable 8. HRs for Cardiovascular Risk, Stratified by ER/PR Status

Outcome	ER/PR Status	Unadjusted HR (95% CI)	Adjusted HR ^a (95% CI)
Coronary artery disease	Positive	0.96 (0.94–0.98)	0.95 (0.93–0.97)
	Negative	1.01 (0.96–1.07)	1.00 (0.95–1.06)
Angina	Positive	0.94 (0.91–0.96)	0.93 (0.90–0.95)
	Negative	0.90 (0.85–0.96)	0.89 (0.84–0.95)
Myocardial infarction	Positive	0.95 (0.92–0.98)	0.94 (0.91–0.98)
	Negative	1.08 (0.99–1.17)	1.07 (0.99–1.17)
Revascularization	Positive	0.88 (0.84–0.92)	0.88 (0.84–0.92)
	Negative	0.91 (0.82–1.01)	0.90 (0.81–1.00)
Sudden cardiac arrest	Positive	1.01 (0.97–1.06)	1.01 (0.97–1.06)
	Negative	1.21 (1.09–1.34)	1.21 (1.08–1.34)
Peripheral vascular disease	Positive	0.92 (0.91–0.94)	0.91 (0.89–0.93)
	Negative	0.98 (0.93–1.03)	0.97 (0.92–1.02)
Stroke	Positive	0.97 (0.96–0.99)	0.97 (0.95–0.98)
	Negative	1.07 (1.03–1.12)	1.06 (1.01–1.11)
Arrhythmia	Positive	1.07 (1.06–1.09)	1.07 (1.05–1.09)
	Negative	1.20 (1.16–1.25)	1.21 (1.16–1.26)
Heart failure	Positive	1.05 (1.03–1.07)	1.04 (1.02–1.06)
	Negative	1.27 (1.22–1.32)	1.26 (1.21–1.31)
Pericarditis	Positive	1.33 (1.27–1.39)	1.34 (1.28–1.40)
	Negative	2.04 (1.85–2.25)	2.08 (1.88–2.31)
Valvular heart disease	Positive	1.06 (1.04–1.08)	1.06 (1.04–1.08)
	Negative	1.31 (1.26–1.37)	1.31 (1.26–1.36)
Venous thromboembolism	Positive	1.51 (1.46–1.57)	1.53 (1.48–1.59)
	Negative	2.04 (1.88–2.22)	2.06 (1.89–2.24)
Deep vein thrombosis	Positive	1.57 (1.51–1.63)	1.59 (1.53–1.66)
	Negative	2.15 (1.97–2.34)	2.17 (1.99–2.37)
Pulmonary embolism	Positive	1.02 (0.91–1.15)	0.96 (0.84–1.09)
	Negative	1.24 (0.95–1.62)	1.28 (0.95–1.72)

Abbreviations: ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.

^aAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease (other than the disease of interest).

Table 9. Rates, Rate Difference, and HRs for Cardiovascular Risk, Using Only Inpatient Claims to Identify Cardiovascular Outcomes

Outcome	Breast Cancer		Noncancer		Rate Difference ^b	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^c
	Events/Follow-Up ^a	Rate (95% CI) ^b	Events/Follow-Up ^a	Rate (95% CI) ^b			
CAD	5,713/382,316	14.94 (14.56 to 15.33)	30,107/1,904,896	15.81 (15.63 to 15.98)	-2.07 (-3.25 to -0.89)	0.95 (0.93 to 0.98)	0.95 (0.93 to 0.98)
Angina	2,086/389,768	5.35 (5.12 to 5.58)	11,522/1,946,468	5.92 (5.81 to 6.03)	-1.44 (-2.14 to -0.74)	0.90 (0.86 to 0.94)	0.89 (0.85 to 0.93)
MI	3,624/391,230	9.26 (8.96 to 9.56)	19,383/1,953,909	9.92 (9.78 to 10.06)	-1.59 (-2.51 to -0.68)	0.95 (0.91 to 0.98)	0.95 (0.92 to 0.98)
Revascularization	2,029/390,229	5.20 (4.97 to 5.43)	11,381/1,946,544	5.85 (5.74 to 5.95)	-1.66 (-2.35 to -0.97)	0.90 (0.86 to 0.94)	0.90 (0.86 to 0.94)
SCA	845/399,149	2.12 (1.97 to 2.26)	4,040/1,999,496	2.02 (1.96 to 2.08)	0.32 (-0.11 to 0.74)	1.07 (0.99 to 1.14)	1.10 (1.03 to 1.18)
PVD	2,889/39,0519	7.40 (7.13 to 7.67)	16,429/1,952,762	8.41 (8.28 to 8.54)	-2.60 (-3.42 to -1.77)	0.88 (0.85 to 0.91)	0.87 (0.84 to 0.91)
Stroke	5,652/384,342	14.71 (14.32 to 15.09)	28,870/1,918,885	15.05 (14.87 to 15.22)	-0.53 (-1.70 to 0.63)	0.97 (0.95 to 1.00)	0.97 (0.95 to 1.00)
Arrhythmia	7,800/372,939	20.91 (20.45 to 21.38)	37,756/1,876,068	20.13 (19.92 to 20.33)	2.68 (1.28 to 4.09)	1.05 (1.02 to 1.07)	1.05 (1.03 to 1.08)
Heart failure	11872/363,165	32.69 (32.10 to 33.28)	57,861/1,822,120	31.75 (31.50 to 32.01)	3.40 (1.62 to 5.18)	1.04 (1.02 to 1.06)	1.03 (1.01 to 1.05)
Pericarditis	724/397,928	1.82 (1.69 to 1.95)	2,734/1,995,304	1.37 (1.32 to 1.42)	1.27 (0.88 to 1.67)	1.33 (1.24 to 1.44)	1.36 (1.26 to 1.46)
VHD	7,164/374,140	19.15 (18.70 to 19.59)	35,104/1,888,069	18.59 (18.40 to 18.79)	2.02 (0.68 to 3.36)	1.03 (1.00 to 1.05)	1.03 (1.01 to 1.05)
VTE	2,205/393,483	5.60 (5.37 to 5.84)	6503/1,984,083	3.28 (3.20 to 3.36)	6.51 (5.82 to 7.19)	1.75 (1.67 to 1.83)	1.78 (1.70 to 1.86)
DVT	2,134/393,567	5.42 (5.19 to 5.65)	6236/1,984,456	3.14 (3.06 to 3.22)	6.37 (5.70 to 7.04)	1.77 (1.69 to 1.85)	1.79 (1.71 to 1.88)
PE	88/399,619	0.22 (0.17 to 0.27)	334/2,002,235	0.17 (0.15 to 0.18)	0.15 (0.02 to 0.29)	1.29 (1.03 to 1.60)	1.25 (0.99 to 1.57)

Abbreviations: CAD, coronary artery disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; PE, peripheral vascular disease; SCA, sudden cardiac arrest; VHD, valvular heart disease; VTE, venous thromboembolism.

^aPerson-years.

^bPer 1,000 patient-years.

^cAdjusted for age, SEER region, time since index, current year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and any other cardiovascular disease (other than the disease of interest).