Original Article

Competing risk analysis of cardiovascular death in breast cancer: evidence from the SEER database

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Background: Cardiovascular disease (CVD) is the leading cause of death for all non-cancer deaths among breast cancer (BC) patients. The aim of this study was to investigate the risk of cardiovascular mortality (CVM) in patients with BC.

Methods: Patients diagnosed with primary BC between 2010 and 2018 were identified through the Surveillance, Epidemiology and End Results (SEER) database. The standardized mortality ratio (SMR) for CVD was calculated to compare the CVM of BC patients with that of the general population. Multivariate competing risk models were performed to identify predictors of CVM in BC patients.

Results: Overall, 399,014 BC patients were included from the SEER database, of whom 7,023 (1.8%) suffered death from CVD. The significantly higher overall SMR of CVM was observed in BC patients [SMR =4.84, 95% confidence interval (CI): 4.72–4.95]. Multivariate competing risk regression analysis revealed that age, race, American Joint Committee on Cancer (AJCC) stage, year of diagnosis, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, BC subtype, surgery, chemotherapy, radiation therapy, and median household income as independent predictors of CVM in BC patients.

Conclusions: Compared to the general population, BC patients have a higher risk of experiencing CVM during the follow-up period after diagnosis. Early detection and intervention of cardiovascular risk factors would improve overall survival (OS) of BC patients.

Keywords: Breast cancer (BC); cardiovascular disease (CVD); cardiovascular mortality (CVM); Surveillance, Epidemiology and End Results (SEER); competing risk regression

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Introduction

According to the 2020 cancer data, 19.3 million new cancers were diagnosed worldwide, among which women with breast cancer (BC) comprised 2.26 million. Female patients with BC contributed approximately 11.7% of all new cancer diagnoses and 24.5% of new cancer diagnoses in women, ranking first in terms of cancer incidence in women. Meanwhile, more than 680,000 people died from BC, accounting for approximately 6.9% of cancer deaths and 15.5% of all cancer deaths among women worldwide,

making it the most life-threatening cancer among women globally (1). Along with medical advances, the majority of BC patients have achieved longer survival and even achieved clinical cures. According to the published literature (2), the 5-year survival rate for BC is as high as 90% and cancer-specific mortality is steadily decreasing, but the proportion of deaths from non-cancer causes among women with BC is increasing (3-5). Therefore, identifying high risk factors for non-cancer deaths such as cardiovascular disease (CVD) (3), infections (6), suicide (7), and diabetes (8) has become critical for BC patients.

CVDs are the leading cause of death globally, with a 21.1% increase in cardiovascular mortality (CVM) from 2007 to 2017 (9). Numerous studies have shown that the prevalence of CVDs is also higher in BC patients than in the general population, and that CVDs are the leading cause of death in BC patients relative to other non-cancer mortality factors (3-5). The American Heart Association (AHA) has reported the existence of several overlapping risk factors for BC and CVDs, such as smoking, poor dietary habits, sedentary lifestyle, diabetes, and obesity (10). The risk of CVD death in BC patients may also be increased by the cardiotoxic effects of treatment such as radiation and chemotherapy (11-13). The most common cardiotoxic effect during BC treatment is left ventricular dysfunction with or without heart failure (12). Especially in elderly patients, the threat of death from CVDs is higher than that of BC (14). Therefore, monitoring, prevention, and secondary management of cardiotoxicity during BC treatment is crucial. Any patients treated for BC, whether the patient has heart disease or not, should be aware of the potential effects of this treatment on their heart. Understanding the risk factors for CVDs in BC patients would play an invaluable role in monitoring and prevention.

To our knowledge, there are relatively few reports on the risk factors for the development of CVM in BC patients. Therefore, in this study, we evaluated the risk and identified independent predictors of CVM in BC patients. We sought to provide a reference for the prevention, monitoring, and management of CVM in patients with BC. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1163/rc).

Highlight box

Key findings

- Breast cancer (BC) patients had a higher risk of cardiovascular mortality (CVM) during follow-up. Age, race, AJCC stage, year of diagnosis, estrogen receptor-status, progesterone receptor-status, human epidermal growth factor receptor 2-status, BC subtype, surgery, chemotherapy, radiation therapy and median household income as independent predictors of CVM in BC patients.

What is known and what is new?

- The prevalence of cardiovascular disease (CVD) is also higher in BC patients than in the general population, and that CVDs are the leading cause of death in BC patients relative to other non-cancer mortality factors.
- We evaluated the risk of experiencing CVM in BC patients and identified independent predictors of CVM in BC patients.

What is the implication, and what should change now?

- Close attention should be paid to cardiovascular adverse events associated with BC treatment. Early detection and intervention of cardiovascular risk factors or CVD can improve the quality of life of BC patients.

Methods

Data source

We collected data from the Surveillance, Epidemiology and End Results (SEER) database for all BC patients from 2010 to 2018 through the SEER*Stat software (version 8.3.9.2; https://seer.cancer.gov/seerstat/). The SEER database is a U.S. population-based cancer registry system that includes incidence, survival, and mortality data. The study did not require ethical approval as the data used were from publicly available information on the SEER database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study population and design

Patients with pathological diagnosis of BC from 2010 to 2018 were obtained for this study. Patients who matched the following characteristics were included: (I) case selection (International Classification of Disease for Oncology/World Health Organization 2008) being 'C500-C509'; (II) primary BC confirmed by puncture or surgical pathology; (III) specific cause of death diagnoses recorded in the SEER database; (IV) with eligible and complete data. The exclusion criteria were as follows: (I) untreated BC patients identified by autopsy or death certificate only; (II) unknown race, age, or sex; (III) unknown American Joint Committee on Cancer (AJCC) stage; (IV) unknown estrogen receptor (ER), progesterone receptor (PR), human epidermal growth

Table 1 Causes of death in breast cancer patients

Non-CVD	CVD
Breast cancer	Diseases of the heart
Other cancers	Hypertension without heart disease
Other non-cancer diseases	Cerebrovascular diseases
	Atherosclerosis
	Aortic aneurysm and dissection
	Other diseases of the arteries, arterioles, and capillaries

CVD, cardiovascular disease.

factor receptor 2 (HER2) status, and BC subtype; (V) no positive histology; (VI) unknown cause of death; (VII) unknown surgery.

Participant variables

Patient variables included age at diagnosis (0–60, 60+), race (White, Black, other), AJCC stage (0, I, II, III, IV), year of diagnosis (2010–2012, 2013–2015, 2016–2018), surgery (no, partial mastectomy, total mastectomy, modified radical mastectomy), ER (positive, negative), PR (positive, negative), HER2 (positive, negative), BC subtype [hormone receptor (HR)+/HER2– (luminal A), HR+/HER2+ (luminal B), HR–/HER2+ (HER2 enriched), HR–/HER2– (triple negative)], chemotherapy (yes, no), radiation therapy (yes, no), median household income (<$60,000, ≥$60,000), and cause of death.

We classified the causes of death in BC as CVD and non-CVD (BC, other cancer, and other non-cancer diseases) (*Table 1*). The main outcome of interest was CVM. CVM was defined as death due to CVD. The follow-up period was from the first diagnosis of BC to the patient's death or the last follow-up.

Statistical analysis

Standardized mortality ratio (SMR) was defined as the ratio of the number of observed deaths in BC patients divided by the expected number of deaths in the general U.S. population during the same time frame. For all SMR calculations, a latency exclusion period of 2 months was allowed. The exact method was used to calculate the 95% confidence interval (95% CI) for all SMRs. CVM was the primary endpoint of the study, and competing events were considered other causes of patient death from non-CVD. Multivariate competing risk survival analyses was used to determine the independent predictors of CVM. All data analyses were performed using R software (version 4.1.1; The R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel 2019 (Microsoft, Redmond, WA, USA). All statistical tests were 2-sided, and P values <0.05 were considered statistically significant.

Results

Patient demographics

Figure 1 shows the diagram of study flow and selection of patients for inclusion. From 2010 to 2018, a total of 56,943 BC patients were excluded due to the initial exclusion/inclusion criteria, and a total of 399,014 BC patients were finally included for the analysis from the SEER database. Meanwhile, 46,390 (11.6%) deaths occurred during follow-up, with the largest number of deaths due to BC (n=28,035 patients), occurring mainly during the 1–5-year follow-up period. This was followed by 9,742 patients who died from other non-cancer diseases, 7,023 patients who died from CVD, and 1,590 patients who died from other cancers. The baseline characteristics are shown in *Table 2* and *Figure 2*. The majority of BC patients were over 60 years old (56.0%), ER positive (ER+; 83.2%), PR positive (PR+; 72.6%), HER2 negative (HER2–; 85.0%), AJCC stage I (48.7%), no chemotherapy (86.6%), and no radiation therapy (71.8%). The predominant ethnicity was White (79.8%), Black (13.9%), and other races (5.2%). Other races include American Indian, Alaska Native, Asian or Pacific Islander, which are collectively referred to as other races due to their small numbers. The subtypes of BC consisted of HR positive (HR+)/HER2– (73.7%), HR+/HER2 positive (HER2+) (10.5%), HR–/HER2+ (4.5%), HR negative (HR–)/HER2– (11.3%). The vast majority of patients underwent surgical treatment, including partial mastectomy (52.3%), total mastectomy (24.7%), modified radical mastectomy (15.5%), and a small number of patients did not undergo surgical treatment. The proportion of risk associated with death from BC gradually decreased during the follow-up period, while the proportion of risk associated with death from other causes gradually increased (*Figure 2*).

Among the 7,023 patients who died from CVD, the leading cause was disease of the heart (73.2%), followed by cerebrovascular disease, hypertension without heart

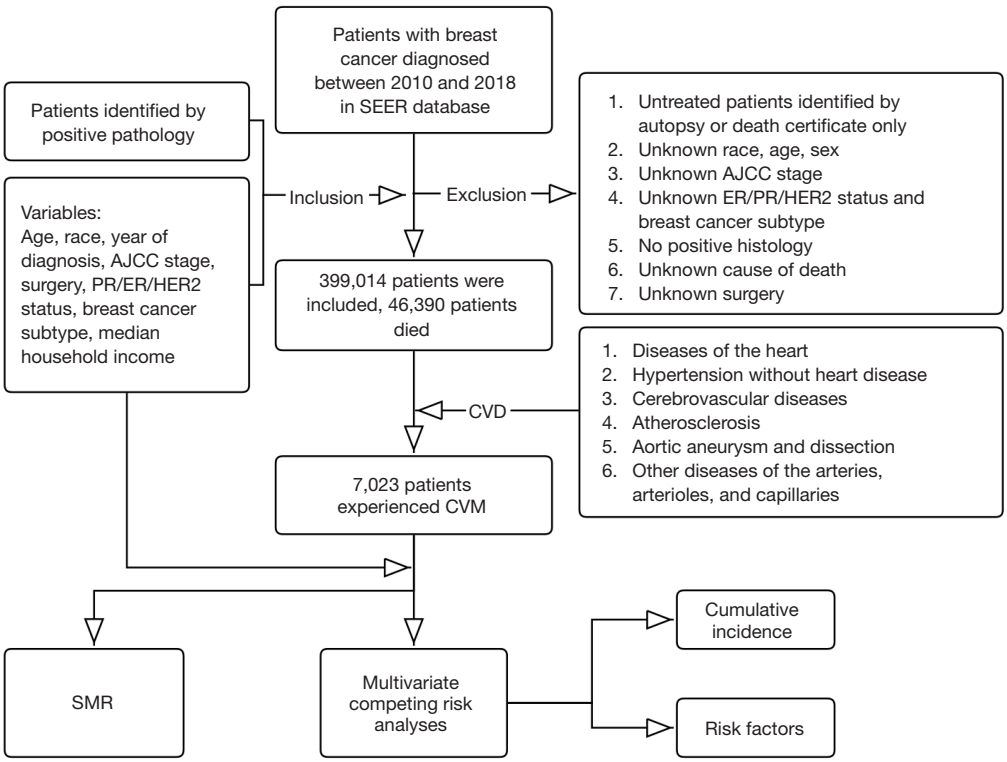

Figure 1 The diagram of study flow and selection of patients for inclusion. SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CVM, cardiovascular mortality; CVD, cardiovascular disease; SMR, standardized mortality ratio.

Table 2 Baseline features and SMRs of CVD in patients with BC

Factors	Observed	Expected	SMR (95% CI)
Overall	7,023	1,452.47	4.84* (4.72–4.95)
Age (years)			
0–60	589	10.33	57.03* (52.52–61.83)
60+	6,434	1,442.14	4.46* (4.35–4.57)
Race			
White	5,681	1,280.67	4.44* (4.32–4.55)
Black	976	123.76	7.89* (7.40–8.40)
Other races	366	48.04	7.62* (6.86–8.44)
AJCC stage (breast)			
0	312	71.78	4.35* (3.88–4.86)
I	2,633	665.23	3.96* (3.81–4.11)
II	2,377	514.09	4.62* (4.44–4.81)
III	748	142	5.27* (4.90–5.66)
IV	953	59.37	16.05* (15.05–17.10)

Table 2 (*continued*)

Table 2 (*continued*)

Factors	Observed	Expected	SMR (95% CI)
Year of diagnosis			
2010–2012	3,987	1,063.04	3.75* (3.64–3.87)
2013–2015	2,325	347.94	6.68* (6.41–6.96)
2016–2018	711	41.5	17.13* (15.90–18.44)
Surgery			
No surgery	1,195	191.56	6.24* (5.89–6.60)
Partial mastectomy	3,355	761.42	4.41* (4.26–4.56)
Total mastectomy	1,364	295.12	4.62* (4.38–4.87)
Modified radical mastectomy	1,109	204.36	5.43* (5.11–5.76)
ER			
Positive	5,976	1,290.58	4.63* (4.51–4.75)
Negative	1,047	161.89	6.47* (6.08–6.87)
PR			
Positive	5,156	1,118.18	4.61* (4.49–4.74)
Negative	1,867	334.29	5.59* (5.33–5.84)
HER2			
Positive	859	142.42	6.03* (5.63–6.45)
Negative	6,164	1,310.05	4.71* (4.59–4.82)
BC subtype			
HR+/HER2– (luminal A)	5,425	1,189.36	4.56* (4.44–4.68)
HR+/HER2+ (luminal B)	617	109.92	5.61* (5.18–6.07)
HR–/HER2+ (HER2 enriched)	242	32.5	7.45* (6.54–8.44)
HR–/HER2– (triple negative)	739	120.69	6.12* (5.69–6.58)
Chemotherapy			
Yes	938	77.97	12.03* (11.38–12.71)
No	6,085	1,380.05	4.41* (4.30–4.52)
Radiation therapy			
Yes	1,979	362.45	5.46* (5.24–5.68)
No	5,044	1,061.57	4.75* (4.62–4.88)
Median household income			
<$60,000	2,720	520.49	5.23* (5.03–5.43)
≥$60,000	4,303	931.98	4.62* (4.48–4.76)

*, P<0.05. SMR, standardized mortality ratio; CVD, cardiovascular disease; BC, breast cancer; 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

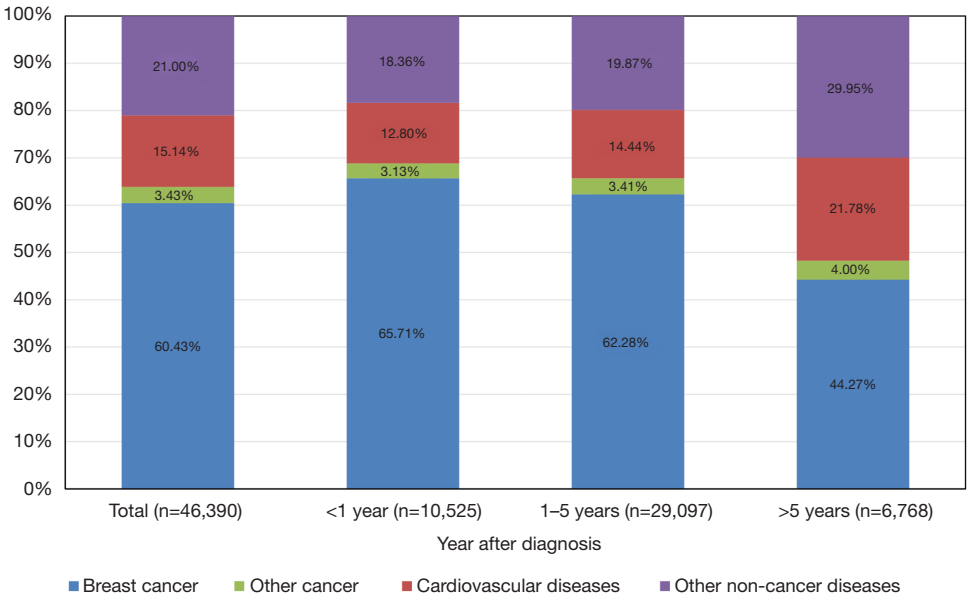

Figure 2 Causes of death in each latency period following breast cancer diagnosis.

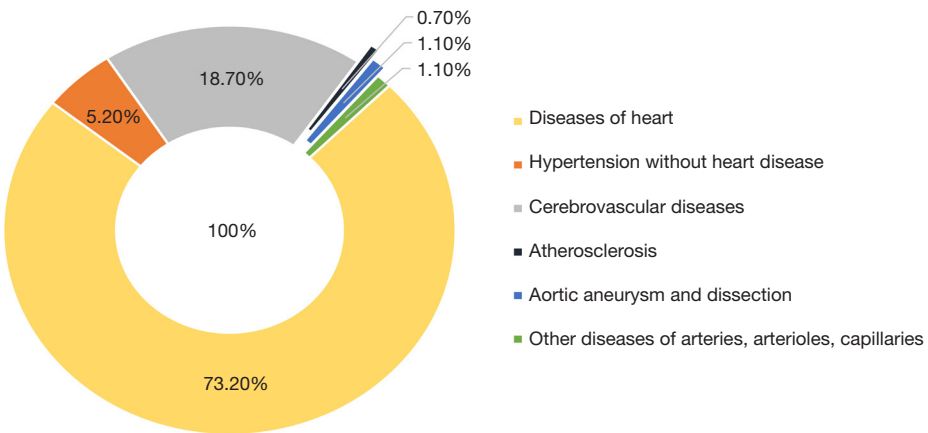

Figure 3 The percentage of deaths due to various cardiovascular disease.

disease, aortic aneurysm and dissection, other diseases of arteries, arterioles and capillaries, and atherosclerosis. The percentage of deaths due to various CVD is shown in *Figure 3*.

The CVD risk in BC patients

The overall SMR for CVM was significantly higher in BC patients compared to the general population (SMR =4.84, 95% CI: 4.72–4.95). Further, CVD-related SMR were increased 57.03-fold (SMR =57.03, 95% CI: 52.52–61.83) in BC patients under 60 years of age, 16.05-fold (SMR =16.05, 95% CI: 15.05–17.10) in BC patients with AJCC stage IV, and 17.13-fold (SMR =17.13, 95% CI: 15.90–18.44) in BC patients diagnosed from 2016 to 2018. *Table 2* shows the subgroup analyses stratified by different variables.

The SMRs of the 6 causes of CVM in BC patients are shown in *Table 3*. The highest SMR was aortic aneurysm and dissection (SMR =6.56, 95% CI: 5.17–8.21), followed by other diseases of the arteries, arterioles, and capillaries (SMR =5.24, 95% CI: 4.12–6.57), atherosclerosis (SMR =4.88, 95% CI: 3.59–6.46), diseases of the heart (SMR

Table 3 The SMRs of six causes of CVM in patients with BC

CVD	Observed	Expected	SMR (95% CI)
Diseases of heart	5141	1062.57	4.84* (4.71–4.97)
Hypertension without heart disease	367	80.98	4.53* (4.08–5.02)
Cerebrovascular diseases	1316	273.18	4.82* (4.56–5.08)
Atherosclerosis	48	9.85	4.88* (3.59–6.46)
Aortic aneurysm and dissection	76	11.58	6.56* (5.17–8.21)
Other diseases of arteries, arterioles, capillaries	75	14.31	5.24* (4.12–6.57)

*, P<0.05. SMR, standardized mortality ratio; CVM, cardiovascular mortality; BC, breast cancer; CVD, cardiovascular disease; 95% CI, 95% confidence interval.

=4.84, 95% CI: 4.71–4.97), cerebrovascular diseases (SMR =4.82, 95% CI: 4.56–5.08), and hypertension without heart disease (SMR =4.53, 95% CI: 4.08–5.02).

Figure 4A shows that the SMR of all causes of death gradually decreased with increasing follow-up time, whereas the SMR of BC was always the highest. *Figure 4B* shows that the SMR in all causes of CVM of BC patients decreased with increasing follow-up time.

Figure 5A shows that the SMR of all causes of death progressively increased with year of diagnosis. *Figure 5B* shows that the SMR in all causes of CVM of BC patients increased with year of diagnosis.

Predictors of death from CVD

As shown in *Table 4*, multivariate competing risk models were used to identify predictors of CVM. The following indicators were identified as being independently associated with higher risks of CVM: age over 60 years [hazard ratio (HR) =5.56, 95% CI: 5.03–6.01, P<0.05], diagnosed between 2016 and 2018 (HR =1.21, 95% CI: 1.16–1.26, P<0.05), underwent partial mastectomy (HR =1.55, 95% CI: 1.43–1.65, P<0.05), HR–/HER2– subtype (HR =1.48, 95% CI: 1.01–1.92, P<0.05). Meanwhile, the following indicators were independently associated with lower risks: other race (HR =0.88, 95% CI: 0.79–0.94, P<0.05), AJCC stage IV (HR =0.05, 95% CI: 0.03–0.10, P<0.05), ER negative (ER–; HR =0.49, 95% CI: 0.38–0.61, P<0.05), PR negative (PR–; HR =0.66, 95% CI: 0.61–0.70, P<0.05), HER2 negative (HER2–; HR =0.62, 95% CI: 0.45–0.81, P<0.05), HR+/HER2+ subtype (HR =0.43, 95% CI: 0.33–0.61, P<0.05), no chemotherapy (HR =0.85, 95% CI: 0.38–1.25, P<0.05), no radiation therapy (HR =0.81, 95% CI: 0.37–1.26, P<0.05), and median household income ≥$60,000 (HR =0.89, 95% CI: 0.81–1.01, P<0.05).

Discussion

For the vast majority of cancer patients, CVD is a major factor in non-cancer mortality (15). In BC patients who are elderly or have underlying disease, CVD is the leading factor in patient mortality (14). By analyzing a large number of BC patients in the SEER database, our findings showed that BC patients had a higher risk of CVM during follow-up compared to the general population (SMR =4.84, 95% CI: 4.72–4.95). The proportion of deaths due to CVD in BC patients gradually increased with increasing follow-up time. Furthermore, we identified age, race, AJCC stage, year of diagnosis, ER status, PR status, HER2 status, median household income, BC subtype, chemotherapy, radiation therapy, and surgery as independent predictors of CVM in BC patients.

Our study found that the risk of CVM was highest in BC patients with less than 1 year of follow-up, as also mentioned in a recent study published in the European Heart Journal (SMR =3.93, 95% CI: 3.89–3.97) (16). The main reason for this may be that BC patients face the challenge of not only the cancer itself, but also the psychological blow of reduced body image due to the absence of the breast/s, which has a serious physical and psychological impact on the patients and aggravates negative emotional reactions such as anxiety, depression, fear, and despair. Some studies have found that CVD such as coronary heart disease, hypertension, and arrhythmia are closely related to psychosocial factors, such as anxiety, depression, and other related adverse emotions (17-19). Interestingly, in our study, we also found that the SMR of CVM gradually increased with increasing year to diagnosis, and we speculate that the reason for this is

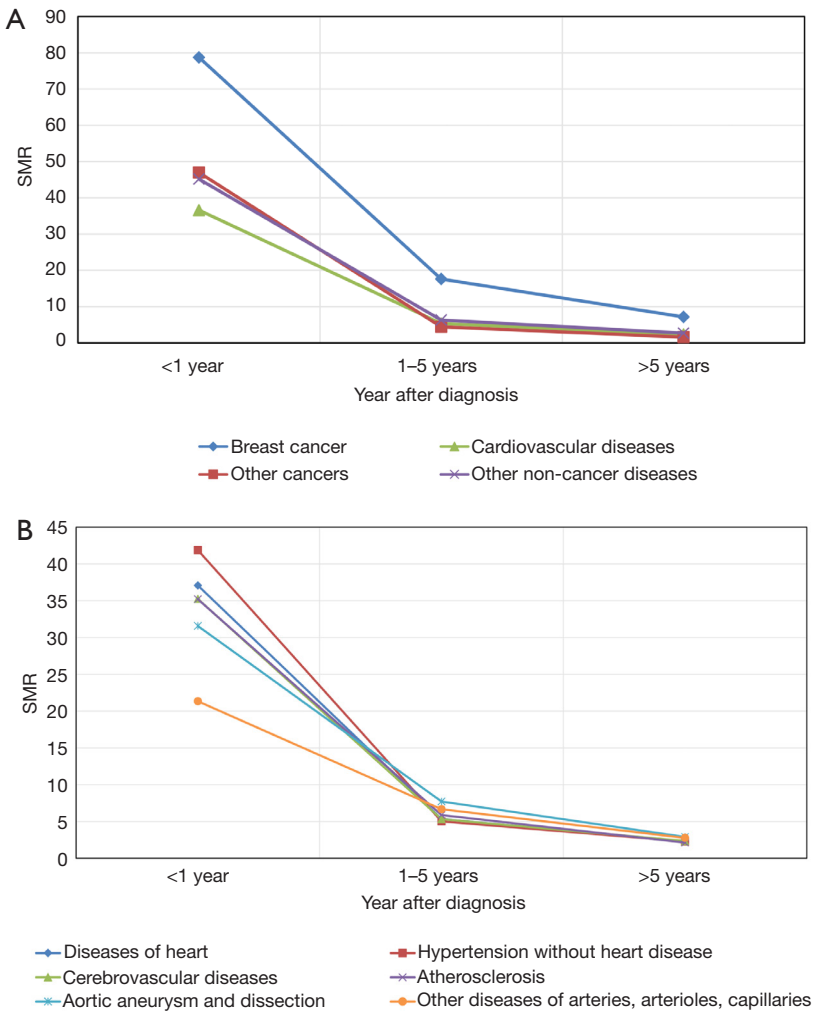

Figure 4 SMR for breast cancer patients at follow-up time. (A) SMR stratified by four causes of death. (B) SMR in cardiovascular disease stratified by all causes of cardiovascular mortality. SMR, standardized mortality rate.

mainly due to the increasing number of novel drugs and chemotherapeutic agents for the treatment of BC with the development of science, such as trastuzumab, tucatinib, talazoparib, everolimus, abemaciclib (20-22), and Keytruda. The use of these novel drugs may increase the incidence of CVD in BC patients.

Multivariate competing risk regression analysis was used to determine independent predictors of CVM in BC patients. Our results showed a higher risk of CVM in older BC patients compared to younger BC patients (HR =5.53, 95% CI: 5.11–5.98), but interestingly, the SMR was higher in younger BC patients (HR =57.03, 95% CI: 52.52–61.83), which was also confirmed in the study by Zaorsky *et al.* (23). Our study also found that other races had lower CVM. Firstly, compared to the White race, other races generally had lower economic and living standards (24), resulting in detection and treatment of BC at a later stage, and thus a higher AJCC stage, with limited treatment options for BC and at a greater risk of death from BC, therefore, not having enough survival time for CVD to be developed or detected.

In addition, our study also found that CVM was lowest in patients with AJCC stage IV and non-operated BC; a possible reason for this is that the vast majority of non-operated BC patients have advanced tumors and their survival time is not long enough to experience CVM. The most recent study reported that the 5-year survival rate for BC patients with AJCC stage I is close to 100%, but only 28% for BC patients with AJCC stage IV (25). At

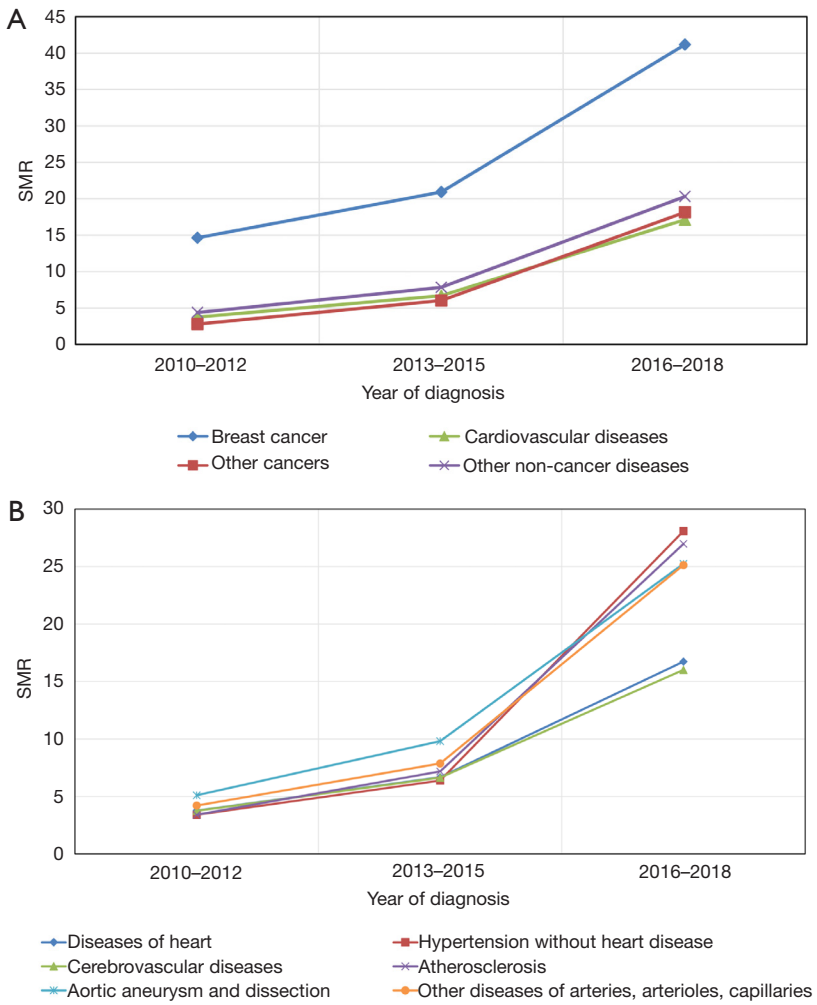

Figure 5 SMR for breast cancer patients at different years of diagnosis. (A) SMR stratified by four causes of death. (B) SMR in cardiovascular disease stratified by all causes of cardiovascular mortality. SMR, standardized mortality rate.

the same time, our study showed that the probability of CVM was lower with increasing year to diagnosis, which may be due to a better understanding of the relationship between CVD and BC and a more focused interest in the prevention and treatment of CVD as society progresses. In our study, patients from low-income families were generally at higher risk of developing CVM, consistent with previous findings (26).

In this study, we included the factors of ER status, PR status, and HER2 status of patients as investigation targets. Multivariate competing risk regression analysis showed that CVM was lower in ER–, PR–, and HER2– BC patients. It is well known that endocrine therapy is the basic adjuvant therapy for patients with HR+ BC. Abnormalities in lipid metabolism have been found in many women using tamoxifen, which may be a preclinical manifestation in patients with atherosclerosis (27). In some early large clinical trials comparing the adverse effects between tamoxifen and letrozole, it was shown that women utilizing letrozole were more likely to develop atherosclerosis than those using tamoxifen (28). Atherosclerosis can lead to thickening and hardening of the arterial walls and narrowing of the lumen, which can further develop into CVD. Trastuzumab is a monoclonal antibody targeting agent mainly used to treat HER2+ BC. Its cardiotoxicity may be related to inhibition of the neuregulin-1/erb-b2 receptor tyrosine kinase signaling pathway, which mainly causes alterations in myocardial contractile proteins and

Table 4 Competing risk analysis for predictors of CVM in patients with BC

Factors	Hazard ratio (95% CI)	P value
Age (years)		
0–60	Reference	Reference
60+	5.56 (5.03–6.01)	<0.05
Race		
White	Reference	Reference
Black	1.03 (0.95–1.06)	0.763
Other	0.88 (0.79–0.94)	<0.05
AJCC stage		
0	Reference	Reference
I	0.55 (0.23–1.32)	0.201
II	0.32 (0.11–0.69)	<0.05
III	0.19 (0.03–0.41)	<0.05
IV	0.05 (0.03–0.10)	<0.05
Year of diagnosis		
2010–2012	Reference	Reference
2013–2015	1.08 (1.03–1.13)	<0.05
2016–2018	1.21 (1.16–1.26)	<0.05
Surgery		
No surgery	Reference	Reference
Partial mastectomy	1.55 (1.43–1.65)	<0.05
Total mastectomy	1.37 (1.25–1.50)	<0.05
Modified radical mastectomy	1.21 (1.13–1.33)	<0.05
ER		
Positive	Reference	Reference
Negative	0.49 (0.38–0.61)	<0.05
PR		
Positive	Reference	Reference
Negative	0.66 (0.61–0.70)	<0.05
HER2		
Positive	Reference	Reference
Negative	0.62 (0.45–0.81)	<0.05
Breast subtype		
HR+/HER2– (luminal A)	Reference	Reference
HR+/HER2+ (luminal B)	0.43 (0.33–0.61)	<0.05
HR–/HER2+ (HER2 enriched)	0.52 (0.50–0.61)	<0.05
HR–/HER2– (triple negative)	1.48 (1.01–1.92)	<0.05
Chemotherapy		
Yes	Reference	Reference
No	0.85(0.38–1.25)	<0.05
Radiation therapy		
Yes	Reference	Reference
No	0.81 (0.37–1.26)	<0.05
Median household income		
<$60,000	Reference	Reference
≥$60,000	0.89 (0.81–1.01)	<0.05

CVM, cardiovascular mortality; BC, breast cancer; 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

mitochondrial structure and function, and rarely myocardial necrosis, usually manifesting as non-dose-related, reversible cardiac insufficiency (29). Study has shown a 12.1% incidence of heart failure in BC patients when treated with trastuzumab alone (10).

We also found that patients with HR+/HER2+ subtype had lower CVM than patients with HR+/HER2– subtype. The main reason for this may be that HR+/HER2– subtype chemotherapy causes a greater cardiovascular risk. Anthracyclines, the most commonly used chemotherapeutic agents for BC, can directly affect cardiac function and can cause type I cardiotoxicity, which is irreversible. However, trastuzumab monoclonal antibody can cause type II cardiotoxicity, which is different from type I cardiotoxicity, and with early detection and early intervention, cardiotoxicity is expected to be reversible. The 8-year follow-up results of the HERA trial suggest that among

patients who had cardiovascular events during 1 year of trastuzumab treatment, 79.5% of cardiac function returned to early standards after ending treatment, indicating that cardiovascular damage caused by trastuzumab is reversible (30). However, either anthracyclines or trastuzumab monoclonal antibody can trigger heart failure in some cases. According to recent research (31), statins work not just to lower cholesterol, but also to reduce oxidative stress and free radical production in heart cells, and the risk of heart failure was significantly lower in women who took statins while receiving anthracycline or trastuzumab monoclonal antibody therapy compared with those who did not take statins prior to cancer treatment. At the same time, we also found that BC patients who received radiotherapy and chemotherapy had higher CVM, which is consistent with the results of many studies (32,33).

In summary, the prognosis of BC patients depends on the cardiovascular health of patients during the whole treatment process. Monitoring changes in patients' cardiac function during the course of treatment can help guide the clinical use of drugs and optimize the treatment plan. For asymptomatic patients who have already received cardiotoxic drugs and have normal cardiac function, regular follow-up of cardiac markers, cardiac ultrasound, and other examinations should be conducted 6–12 months and 2 years after treatment. Patients who experience CVD after treatment should be given long-term treatment with drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, as well as regular cardiac examinations (34). Meanwhile, the AHA guideline also puts forward the ABCDE 5-step approach to prevent CVD in BC patients (35), advocating the "7 Simple Lives": increasing physical activity, healthy weight, healthy diet, avoiding tobacco, and maintaining normal blood pressure, blood glucose, and blood lipids, which can significantly reduce the risk of CVD and lower the incidence of BC.

There are some limitations in this study. First, due to database limitations, we were unable to obtain data on smoking, alcohol consumption, body mass index, specific chemotherapy regimens, and whether or not statins were taken to prevent CVD, which had an impact on our study. Secondly, the retrospective database-based non-randomized design of this study may have introduced selection bias for patients. Third, although the SEER database includes nearly 30% of the US population, it is still not representative of the entire population, and we need a large follow-up cohort study to validate our findings.

Conclusions

Compared to the general population, BC patients had a higher risk of CVM during follow-up. Patients who were diagnosed over 60 years of age, of other races, AJCC stage 0, diagnosed between 2016 and 2018, undergoing partial mastectomy, ER+, PR+, HER2+, HR–/HER2– subtype, receiving chemotherapy or radiation therapy, and median household income <$60,000, had a significantly increased risk of CVM. Our findings suggest that close attention should be paid to cardiovascular adverse events associated with BC treatment. Early detection and intervention of cardiovascular risk factors or CVD can improve the quality of life of BC patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study did not require ethical approval as the data used were from publicly available information on the SEER database.

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