Increased risk of cardiovascular death in breast cancer patients without chemotherapy or (and) radiotherapy: a large population-based study.

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Abstract

Background

Cardiovascular death (CVD) in breast cancer patients without chemotherapy or (and) radiotherapy has not been studied yet. This study evaluates the correlation between breast cancer and CVD risk independent of chemotherapy (CT) or (and) radiotherapy (RT).

Methods

Data of female breast cancer patients without receiving CT or RT were retrieved from the Surveillance, Epidemiology, and End Result (SEER) database (2004–2015). Data were divided into two cohorts: Patients who underwent tumor resection (resection cohort) and those who didn't undergo resection (no resection cohort). The CVD risk in patients was expressed as standardized mortality ratios (SMRs). A 1:1 propensity score matching (PSM) was applied to balance inter-group bias, and competing risk regressions were utilized to evaluate the impact of tumor resection on CVD.

Results

The CVD risk was significantly higher (SMR = 2.196, 95% CI:2.148–2.245, $P < 0.001$) in breast cancer patients who did not receive CT or RT compared to the general population. Breast cancer patients who did not undergo tumor resection showed a higher CVD risk than patients who underwent tumour resection (tumor resection SMR = 2.031, 95% CI: 1.983–2.079, $P < 0.001$; no resection SMR = 5.425, 95% CI:5.087–5.781, $P < 0.001$). After PSM, the CVD risk among patients without tumor resection indicated an increase of 1.165-fold compared to the patients with tumor resection (HR = 1.165, 95% CI: 1.039–1.306, $P = 0.009$).

Conclusions

Female breast cancer patients are at higher risk of CVD despite unexposure to cardio-toxic CT or RT. However, female breast cancer patients subjected to tumor resection have decreased CVD risk. This study suggests that monitoring female breast cancer patients not receiving RT or CT might serve as a preventative measure against CVD.

Background

Breast cancer is a serious common threat for women health, accounting for 30% of new cancer cases in females, and is on a growing trend.(1, 2). Rapid advances in cancer screening and treatment technologies increased the five-year survival rate to 90%.(1) By 2014, the estimated number of breast cancer survivors reached over 3.1 million in the United States and anticipated to rise to more than 3.9 million by 2024(3). However, cardiovascular diseases as appear to be a life-threatening complication for the survivors.

Cardiovascular death (CVD) is becoming the leading cause of death in breast cancer survivors(4, 5). Identifying the population at high risk of CVD is a key step in implementing routine preventative measures to improve breast cancer survivors' prognosis.

At the present, the mainstream belief among cardio-oncologists is that cardiotoxic therapies, including chemotherapy (CT) or radiotherapy (RT) are the main contributors to increased risk of CVD in breast cancer survivors(6, 7). The clinical guidelines of American Society of Clinical Oncology (ASCO)(8) limit the target population needing prevention and monitoring of cardiac dysfunction to those who have accepted cardiotoxic therapies. However, the target population mentioned in ASCO is restricted, and the guideline might neglect CVD risk among cancer patients who opted out of cardiotoxic therapies.

Previous studies indicate that CVD risk might also be higher among breast cancer patients not exposed to CT or RT. A recent study revealed that breast cancer survivors suffered elevated CVD risk(9). Furthermore, a population-based study also showed that CVD risk of breast cancer survivors was apparently higher than that of the general population(10). These two studies evaluated CVD risk in breast cancer survivors regardless of the treatment regimen (with or without CT/RT). Surprisingly, another study reported no increase in CVD risk among breast cancer survivors pretreated with CT/RT to the general population.(11) These results suggest that elevated CVD risk among breast cancer survivors is resulting in part from survivors not exposed to CT or RT. A single-center study supported this possibility and found decreased cardiac function among cancer patients not exposed to CT or RT.(12) Another study also revealed that tumors could directly induce cardiovascular damage by tumor-induced inflammation in tumor-bearing mice(13). The cardiotoxicity of CT and RT in breast cancer patients is confirmed, but it remains elusive whether avoiding CT and/or RT regimens lower or increase CVD risk in breast cancer survivors. This calls for urgent need to evaluate, by large-scale population-based study, the CVD risk among breast cancer patients who opted out of the CT and/or RT treatments.

This study evaluates the CVD risk among breast cancer patients who opted out of the CT or (and) RT treatments and are documented in the Surveillance, Epidemiology, and End Result-18 (SEER-18) database. The analysis aims to achieve three objectives. Objective 1 is to evaluate CVD risk of breast cancer patients who never received CT or RT in comparison to the general population. Objective 2 is to evaluate CVD risk of breast cancer patients who never received CT or RT and were either subjected or not to tumor resection in comparison to the general population. Objective 3, is to conduct internal comparisons among breast cancer patients, aiming to reduce treatment selection bias and evaluate the independent effect of tumor removal on the CVD risk in breast cancer patients who never received CT or RT. The study aims at updating the guidelines of which breast cancer population requires prevention and monitoring for CVD risk.

Patients And Methods

Data source

In this registry-based cohort study, the data of breast cancer patients were obtained from the SEER-18 database, an authoritative program providing 18 cancer registries data and covering approximately 34.6 percent of the American population (http://seer.cancer.gov/). The SEER database has been frequently used for cardio-oncology studies(9, 10, 14, 15). To compare with the cohort derived from the SEER database, the referred standardized population cohort was retrieved from Wide-ranging Online Data for Epidemiologic Research of the Centers for Disease Control and Prevention (CDC WONDER). CDC WONDER shares data of the general American population, which is based on death certificates of American residents. Ethical approval of this publicly available information was not required.

Study population and design

Only the female breast cancer patients without chemotherapy (CT) or radiotherapy (RT) were included in this study. The inclusion criteria were as follows: (1) case selection (site and morphology, primary site-labeled) = 'C50.x'; (2) with pathological diagnosis between 2004 and 2015; (3) patients with only one primary tumor; (4) patients with active follow-up. The exclusion criteria were as follows: (1) history of CT or RT; (2) unknown causes of deaths; (3) male patients; (4) age at diagnosis under 45 years old; (5) unknown stage according to the American Joint Committee on Cancer (AJCC) staging system; (6) unknown surgery (Figure 1). Patients under 45 years old were excluded due to their very low number(14). After the inclusion and the exclusion criteria, we established an overall cohort.

Firstly, for Objective 1, CVD risk in 10-year age-stratum (45-54, 55-64, 65-74, 75-84, 85+) of the overall cohort was compared to that of the age-matched U.S. female population, which was expressed as standardized mortality ratio (SMR). Secondly, for Objective 2, the overall cohort was categorized into two cohorts according to surgical resection: tumor resection cohort and no resection cohort. We compared the CVD risk between the tumor resection cohort and the no resection cohort by using SMR. Thirdly, for Objective 3, participants were further excluded from the overall patients if they had unknown or unspecific information regarding their marital status, race, grade, estrogen receptor (ER) status and progesterone receptor (PR) status. Patients with paired tumor site or unspecific tumor site were also excluded owing to their very low number. Then resection selection cohort were extracted and further divided into two sub-cohorts: tumor resection sub-cohort and no resection sub-cohort (Figure 1).

Participant variables and outcomes

Patient variables include surgery (tumor resection and no resection), age at diagnosis (45-60 years, >60 years), race (white, non-white), marital status (married, unmarried), laterality (left, right), grade (high, low), ER status (positive, negative), PR status (positive, negative), HER2 status (positive, negative, unknown) and AJCC stage(4) (I, II, III and IV).

We classified cause of death as CVD or non-CVD. The CVD was defined as deaths due to heart disease (I00-I09, I11, I13, I20-I51), hypertension without heart disease (I10, I12), cerebrovascular disease (I60-I69), atherosclerosis (I70), aortic aneurysm and dissection (I71) and other diseases of arteries, arterioles and capillaries (I72-I78), according to the International Classification of Disease-10 (ICD-10) codes.(14, 15)

The non-CVD contained patients died from other causes and was considered as the competing events against CVD. Patients who survived till the last follow-up were treated as censored observations.

Statistical analysis

χ2 test was used to evaluate categorical variables in baseline characteristics. SMR was defined as the ratio of the observed deaths to the expected(16). The expected number of deaths were calculated according to the following formula: expected deaths = person-years × mortality rate of CVD among general population, where the mortality rate of CVDs is available on CDC WONDER(15), and the person-years is the sum of patients' survival time, from the date of breast cancer diagnosis to the date of study completion (December 31st, 2015) or the date of CVD. Ninety-five percent confidence intervals (95% CIs) and *P* value of SMRs were calculated by using the methods by Rothman-Boice(16) and by Altman *et al*(17), respectively.

To reduce potential imbalance between breast patients who received tumor resection and no resection, a 1:1 propensity score matching (PSM) was applied. The PSM was performed using logistic regression and nearest neighbor method with caliper width of 0.01. PSM should match the confounding variables instead of all baseline variables.(18) The potential confounding variables used for matching included age at diagnosis, marital status, grade, ER status, PR status, HER2 status and AJCC stage. The balances between matched covariates were acceptable if *P* values were greater than 0.05.(19)

Further, the univariate and multivariate Fine and Gray's competing risks regressions were used to evaluate the independent effect of tumor resection on the CVD risk among breast cancer patients without CT or RT. The Fine and Gray's competing risks regression was performed to account for the two competing events: CVD deaths and non-CVD deaths.

χ2 test and PSM were analyzed using SPSS version 25.0 (SPSS, Chicago, IL) and R software version 3.6.1 (https://www.r-project.org), respectively. Fine and Gray's competing risks regression was conducted using Stata version 15 (Stata Corp, College Station, TX, USA). A two-tailed *P* value < 0.05 was considered statistically significant.

Results

Patient selections and baseline characteristics

A total of 131,306 female breast cancer patients without CT or RT between 2004 and 2015 were included in this study, of whom the tumor resection cohort included 117,012 (89.1%) patients and the no resection cohort included 14,294 (10.9%) patients. After further selection, the resection cohort consisted of 106,326 breast cancer patients.

Compared to patients without tumor resection, patients with resection were more likely to be younger, married, white, ER-positive, PR-positive, HER2-unknown, and have lower grade, left breast cancer and have

lower AJCC stage (Table S1). The average follow-up time was 51.9 months among 131,306 breast cancer patients.

The CVD risk in breast cancer patients and general population

The CVD-related SMR was significantly higher in breast cancer patients without CT or RT (SMR=2.196, 95% CI: 2.148-2.245, *P*<0.001) compared to the general population. In all age strata (45-84 years old), breast cancer patients without CT or RT had a higher CVD risk than the general population at the same age (all *P*<0.001) (Figure 2 and Table S2).

Further, CVD-related SMRs were increased to 2.031 folds (SMR=2.031, 95% CI: 1.983-2.079, *P*<0.001) and 5.425 folds (SMR=5.425, 95% CI: 5.087-5.781, *P*<0.001) in breast cancer patients with tumor resection and without resection respectively, compared to the general population. In all age strata (45-84 years old), the increased extent of CVD-related SMRs was all higher in patients without resection compared to the patients with tumor resection (no resection SMRs:1.603-6.500; tumor resection SMRs: 1.113-2.037) (Figure 3 and Table S2).

Propensity score-matched analysis

Of the 106,326 breast cancer patients selected for internal comparisons, 97,496 (91.7%) received tumor resection and 8830 (8.3%) did not. Before PSM, the variables (age at diagnosis, race, marital status, grade, ER status, PR status, HER2 status, AJCC stage) showed imbalanced between the two groups (all *P*< 0.05). After the 1:1 PSM, 17,478 patients were included in the matched cohort, and the confounding covariates became balanced between the two groups (Table 1). Laterality and race were not allocated in PSM, the former was balanced but the later was imbalanced before and after PSM. However, race had no confounding effect on the results after PSM (Table 2 and Table S4).

Competing risk regressions in internal comparisons

In univariate analysis before PSM and after PSM, tumor resection, age at diagnosis, marital status, PR status and HER2 status were correlated with CVD among breast cancer patients (Table 2). The breast cancer patients without tumor resection showed increased CVD risk compared to the patients with tumor resection (after PSM, unadjusted HR=1.140, 95% CI:1.017-1.279, *P*=0.025). To eliminate the possibility of producing false positive results, regression analysis of multivariate competing risks was performed and the tumor resection was confirmed as an independent risk factor that influences CVD both before PSM and after PSM. Adjustment for cofounding covariates (model 1: age at diagnosis, marital status, PR status and HER2 status) indicated a robust adjusted hazard ratio (HR) of no resection after PSM (in model 1, adjusted HR=1.165, 95% CI:1.039-1.306, *P*=0.009). After further adjustment (model 2: all covariates in the baseline), adjusted HR did not change distinctively and the CVD risk among patients without tumor resection increased to 1.166-fold compared to patients with tumor resection (in model 2, adjusted HR=1.166, 95% CI:1.040-1.308, *P*=0.009) (Table 3,Table S3 and Table S4).

Discussion

To the best of our knowledge, this is the first population-based study focusing on CVD risk among breast cancer survivors without CT or RT. We found that the CVD risk was increased by 2.196-fold in breast cancer patients without CT or RT compared to the general population. Previous SEER-based studies demonstrated that overall breast cancer survivors (including those with or without CT or RT) had higher CVD risk compared to the general population(9, 10). The contributing factors for CVD risk in patients with breast cancer are as follows: Many previous studies revealed cancer treatment-related cardiotoxicity(20), such as that from CT(6) and RT(7). However, these studies neglected the CVD risk in breast cancer patients who opted out of CT or RT. Interestingly, we found that breast cancer patients who did not receive CT or RT also suffered higher CVD risk than the general population, suggesting that CVD risk in breast cancer patients may increase independently of cardiotoxic therapies. On the other hand, due to lack of detailed information on cardiovascular complications of SEER itself, the other cardiac causes of CVD among patients with breast cancer is unclear besides cardiotoxicity. A recent study on breast cancer related cardiovascular risk by Greenlee *et al.*(21) indicated that breast cancer patients suffered from increased risk of cardiovascular related diseases such as cardiac arrest, heart failure, cardiomyopathy, venous thromboembolism and carotid disease, which may be further led to elevated CVD risk.

In accordance with the results of this study, Pavo *et al.*(22) found that myocardial damage was directly linked to cancer, and myocardial damage biomarkers were upregulated in cancer patients who did not undergo cardiotoxic therapies. Likewise, a retrospective study revealed that cancer patients without CT or RT had a higher risk of cardiac dysfunction than the age- and gender-matched controls(12). However, these studies were limited due to small sample size, whereas this study included large-scale and multicenter cases. Although cardiovascular comorbidities of the research subjects could not be taken into account in this study, the compared general population also included those with or without cardiovascular comorbidities. The comparison performed by using SMR analysis, which is widely used in similar studies,(9, 11, 15) may balance out the effect of pre-existing cardiovascular comorbidities. Moreover, the majority of the subjects accepted surgery, which indicated that they had less possibility of having serious cardiovascular comorbidities. These findings highlighted the CVD risk among breast cancer survivors without CT or RT, and the importance of monitoring and preventing CVD in these survivors. We speculate that the tumor itself, not merely the cardiotoxicity of CT or RT, may increase CVD risk among chemoradiotherapy-free patients.

If the speculation that tumors can induce CVD risk is indeed tenable, a reduction of CVD risk may show among breast cancer patients who undergone tumor resection. We found that tumor-resection group had significantly decreased CVD risk compared to tumor-bearing group (tumor resection SMR: 2.031; no resection SMR: 5.425). Nevertheless, the confounding covariates should be taken into account as they may affect the therapeutic approach of choice and the CVD risk, which may cause treatment selection bias and false positive results. To control for this bias, we further utilized PSM to balance the confounding factors and performed competing risk regressions to verify the independent effect of tumor resection on CVD. After PSM, we obtained a robust result, showing that the CVD risk among patients

without tumor resection increased by 1.165-fold compared to patients with tumor resection (in model 1, adjusted HR=1.165; in model 2, adjusted HR=1.166, both $P<0.05$). The change in regression coefficients of tumor resection were not obvious after PSM, which indicated that PSM was reliable to balance the basic condition of patients(23). Although we could completely adjust for all potential confounding variables, we made the greatest efforts to verify our results. These findings should be cautiously interpreted. Our study was consistent with a previous study showing significantly decreased CVD risk for cancer survivors who undergone surgery compared with the no-surgery group.(24) However, tumor resection was just a covariate in the previous study(24). The present study provides stronger evidence for the correlation between CVD risk and tumor resection. Our results further support the speculation that existing breast cancer might strongly correlate with higher CVD risk.

Interestingly, even though breast cancer patients were treated with tumor resection, they still had residual CVD risk compared to the general population (SMRs=1.113-2.037, all $P < 0.001$). This may be attributable to the overlapping risk factors of cardiovascular diseases and breast cancer, such as chronic systemic low-grade inflammation,(25) hyperlipidemia, high cholesterol intake and genetic risk factors,(26) which cannot be reversed completely by tumor resection. Further studies on the residual CVD risk among cancer patients are needed.

The mechanisms underlying higher CVD risk among breast cancer survivors without CT or RT remain obscure, but the hypothetical explanations may lie in cancer-induced CVD. On the one hand, our PSM-adjusted results support the speculation that breast cancer-bearing patients are at higher CVD risk, whereas the risk could be remarkably reduced after tumor resection. On the other hand, further supporting evidence comes from basic research reporting that tumor-induced inflammation might increase CVD risk. Breast cancer could damage the cardiovascular system of breast cancer-bearing mice by initiating systemic inflammatory reactions named neutrophil extracellular traps (NETs).(27) Cancer-induced NETs could accumulate in the heart and systemic vasculature to induce cardiac dysfunction and vascular dysfunction(13, 28, 29). NETs could also promote cancer-associated thrombosis and further causing ischemic strokes(27, 30). Based on the postulation that tumor-induced inflammation may increase CVD risk, anti-inflammatory drugs should decrease CVD risk. Furthermore, clinical evidences that strengthen our hypothesis come from the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS),(31, 32) which showed that anti-inflammatory drugs could reduce both cancer mortality and CVD. In addition, other contributing factors might include cancer-related hypercoagulability,(33, 34) tumor metastasis to the cardiovascular system,(35) oxidative stress(36) and nitric oxide-dependent endothelial impairment(37). Nevertheless, the interpretations to our data remain speculative and further study is needed to investigate the underlying mechanisms.

Strength and limitations

The strengths of the present study are noteworthy for its large-scale population, long-term follow-up and the relatively rigorous statistical analysis. To the best of our knowledge, this is the first study to report that breast cancer survivors without CT or RT are inflicted by increased CVD risk on the population level.

Some limitations of the study should be taken into account. Firstly, this is a retrospective non-randomized study which may have selection bias for patients. Nevertheless, we used PSM to resolve this limitation as much as possible. Secondly, the data on cardiovascular risk factors and cardiovascular disease history was not provided by the SEER, and we could not distinguish their effects on CVD risk in our SEER-based study. To address this issue, we used CVD-related SMR in comparing the general population with or without cardiovascular conditions. Thirdly, the SEER registries do not provide detailed information on whether chemotherapy includes systemic therapy, targeted therapy or hormonal therapy. Lastly, some information of patients accepting CT or RT was missing and was then coded as “no/unknown”, a code supposed to represent the missing information about CT and RT for patients. This raised an issue that our cohort might contain some “no/unknown” patients who actually accepted CT or RT. Nevertheless, the incidence of this type of miscoded patients was less than 8% (CT: 7.7%; RT: 7.4%), suggesting SEER information had sufficient specificity and reliability(11, 38).

Conclusions

This study found that breast cancer survivors free of CT or RT were at higher CVD risk, and tumor resection might be a contributing factor to decreased CVD risk in breast cancer survivors. Existing breast cancer might strongly correlate with higher CVD risk. Clinical practices highlight that breast cancer survivors free of CT or RT should also be targets for monitoring of CVD risk and prevention of the disease. Clinicians should start to monitor CVD risk and prevent CVD once breast cancer is diagnosed. Further studies and prospective trials are needed to verify our conclusions and to explore the underlying mechanisms.

Abbreviations

AJCC: American Joint Committee on Cancer; ASCO: American Society of Clinical Oncology; CDC WONDER: Wide-ranging Online Data for Epidemiologic Research of the Centers for Disease Control and Prevention; CI: Confidence interval; CT: Chemotherapy; CVD: Cardiovascular death; ER: Estrogen receptor; HR: Hazard ratio; NET: Neutrophil extracellular trap; PR: Progesterone receptor; PSM: Propensity score matching; RT: Radiotherapy; SEER: Surveillance, Epidemiology, and End Result database; SMR: Standardized mortality ratio

Declarations

Ethics approval and consent to participate

A Data-Use Agreement Form was sent to the National Cancer Institute’s SEER Program for obtaining the de-identified SEER dataset. Ethical approval of these publicly available information is not required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available in the SEER database (https://seer.cancer.gov/data/access.html).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Tianwang Guan: Conception, study design, data collection, analysis, interpretation of results, figure design, article draft writing, article–review and editing; **Hanbin Zhang** and **Jinming Yang**: study design, data collection, analysis, interpretation of results, article draft writing, article–review and editing; **Wenrui Lin** and **Kenie Wang**: interpretation of results and figure design, **Miao Su** and **Weien Peng**: article draft writing; **Weien Peng**, **Yemin Li** and **Yanxian Lai**: study design and data collection; **Cheng Liu**: Funding acquisition, interpretation of results, project administration and supervision, article–review and editing. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics before and after propensity score matching.

ıle	Before PSM (N/%)			After PSM (N/%)		
	No resection	Tumor resection	*P*	No resection	Tumor resection	*P*
	8,830	97,496		8,739	8,739	
diagnosis			< 0.001			0.688
60 years	2,205 (25.0)	32,652 (33.5)		2,197 (25.1)	2,174 (24.9)	
0 years	6,625 (75.0)	64,844 (66.5)		6,542 (74.9)	6,565 (75.1)	
			< 0.001			< 0.001
ıte	6,737 (76.3)	80,127 (82.2)		6,668 (76.3)	7,079 (81.0)	
n-White [a]	2,093 (23.7)	17,369 (17.8)		2,071 (23.7)	1,660 (19.0)	
l status			< 0.001			0.610
:ried	3,014 (34.1)	49,752 (51.0)		2,991 (34.2)	3023 (34.6)	
narried	5,816 (65.9)	47,744 (49.0)		5,748 (65.8)	5716 (65.4)	
lity			0.173			0.193
	4,587 (51.9)	49,909 (51.2)		4,535 (51.9)	4,449 (50.9)	
ht	4,243 (48.1)	47,587 (48.8)		4,204 (48.1)	4,290 (49.1)	
[b]			<0.001			0.961
v	5,940 (67.3)	73,488 (75.4)		5,875 (67.2)	5,878 (67.3)	
h	2,890 (32.7)	24,008 (24.6)		2,864 (32.8)	2,861 (32.7)	
tus			< 0.001			1.000
itive	7,504 (85.0)	85,372 (87.6)		7,431 (85.0)	7,431 (85.0)	
gative	1,326 (15.0)	12,124 (12.4)		1,308 (15.0)	1,308 (15.0)	
tus			< 0.001			0.092
itive	6,410 (72.6)	74,900 (76.8)		6,350 (72.7)	6,250 (71.5)	
gative	2,420 (27.4)	22,596 (23.2)		2,389 (27.3)	2,489 (28.5)	
status			<0.001			0.296
itive	868 (9.8)	4,525 (4.6)		798 (9.1)	788 (9.0)	
gative	4,979 (56.4)	46,354 (47.5)		4,958 (56.7)	4,870 (55.7)	
:nown	2,983 (33.8)	46,617 (47.8)		2,983 (34.1)	3,081 (35.3)	
stage			< 0.001			0.563
	1,958 (22.2)	58,956 (60.5)		1,958 (22.4)	1,908 (21.8)	
	2,455 (27.8)	31,204 (32.0)		2,455 (28.1)	2,505 (28.7)	
ınd IV	4,417 (50.0)	7,336 (7.5)		4,326 (49.5)	4,326 (49.5)	

[#] Non-White includes Black/American Indian/Alaska Native and Asian/Pacific Islander.

*Low (Grade I: well differentiated and Grade II: moderately differentiated) and high (Grade III: poorly differentiated and Grade IV: undifferentiated).

Abbreviations: ER, estrogen receptor; HER2, human epidermal receptor 2; PR, progesterone receptor; PSM, propensity score matching.

Table 2. Regression analysis of univariate competing-risks for cardiovascular death.

Variable	Before PSM		After PSM	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Tumor resection				
Yes	Reference		Reference	
No dissection	1.468 (1.345-1.603)	< 0.001	1.140 (1.017-1.279)	0.025
Age at diagnosis				
45- 60 years	Reference		Reference	
> 60 years	12.789 (11.236-14.556)	< 0.001	8.444 (6.270-11.374)	< 0.001
Race				
White	Reference		Reference	
Non-White [a]	0.837 (0.781-0.898)	< 0.001	0.916 (0.791-1.062)	0.245
Marital status				
Married	Reference		Reference	
Unmarried	2.616 (2.475-2.765)	< 0.001	1.934 (1.681-2.226)	< 0.001
Laterality				
Left	Reference		Reference	
Right	0.964 (0.917-1.013)	0.147	0.930 (0.828-1.044)	0.220
Grade [b]				
Low	Reference		Reference	
High	0.955 (0.903-1.010)	0.109	0.882 (0.778-1.000)	0.051
ER status				
Positive	Reference		Reference	
Negative	0.984 (0.915-1.058)	0.664	0.849 (0.714-1.010)	0.065
PR status				
Positive	Reference		Reference	
Negative	1.054 (0.996-1.115)	0.070	0.831 (0.727-0.950)	0.007
HER2 status				
Positive	Reference		Reference	
Negative	0.915 (0.778-1.077)	0.286	0.989 (0.761-1.286)	0.935
Unknown	1.265 (1.081-1.480)	0.003	1.560 (1.210-2.013)	0.001
AJCC stage				
I	Reference		Reference	
II	1.445 (1.370-1.525)	< 0.001	1.139 (0.972-1.335)	0.109
III and IV	1.444 (1.334-1.562)	< 0.001	0.869 (0.748-1.009)	0.065

[#]Non-White includes Black/American Indian/Alaska Native and Asian/Pacific Islander.

*Low (Grade I: well differentiated and Grade II: moderately differentiated) and high (Grade III: poorly differentiated and Grade IV: undifferentiated).

Table 3. Regression analysis of multivariate competing-risks for cardiovascular death.

Variable	Before PSM		After PSM	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Unadjusted HR				
Tumor resection	Reference		Reference	
No resection	1.468 (1.345-1.603)	< 0.001	1.140 (1.017-1.279)	0.025
Model 1[a]				
Tumor resection	Reference		Reference	
No resection	1.303 (1.191-1.427)	< 0.001	1.165 (1.039-1.306)	0.009
Model 2 [b]				
Tumor resection	Reference		Reference	
No resection	1.272 (1.147-1.411)	< 0.001	1.166 (1.040-1.308)	0.009

[#] Model 1: hazard ratios (HRs) were adjusted for statistically significant factors according to univariate analysis (age at diagnosis, marital status, PR status and HER2 status).

*Model 2: hazard ratios were adjusted for all factors in the baseline.

Figures

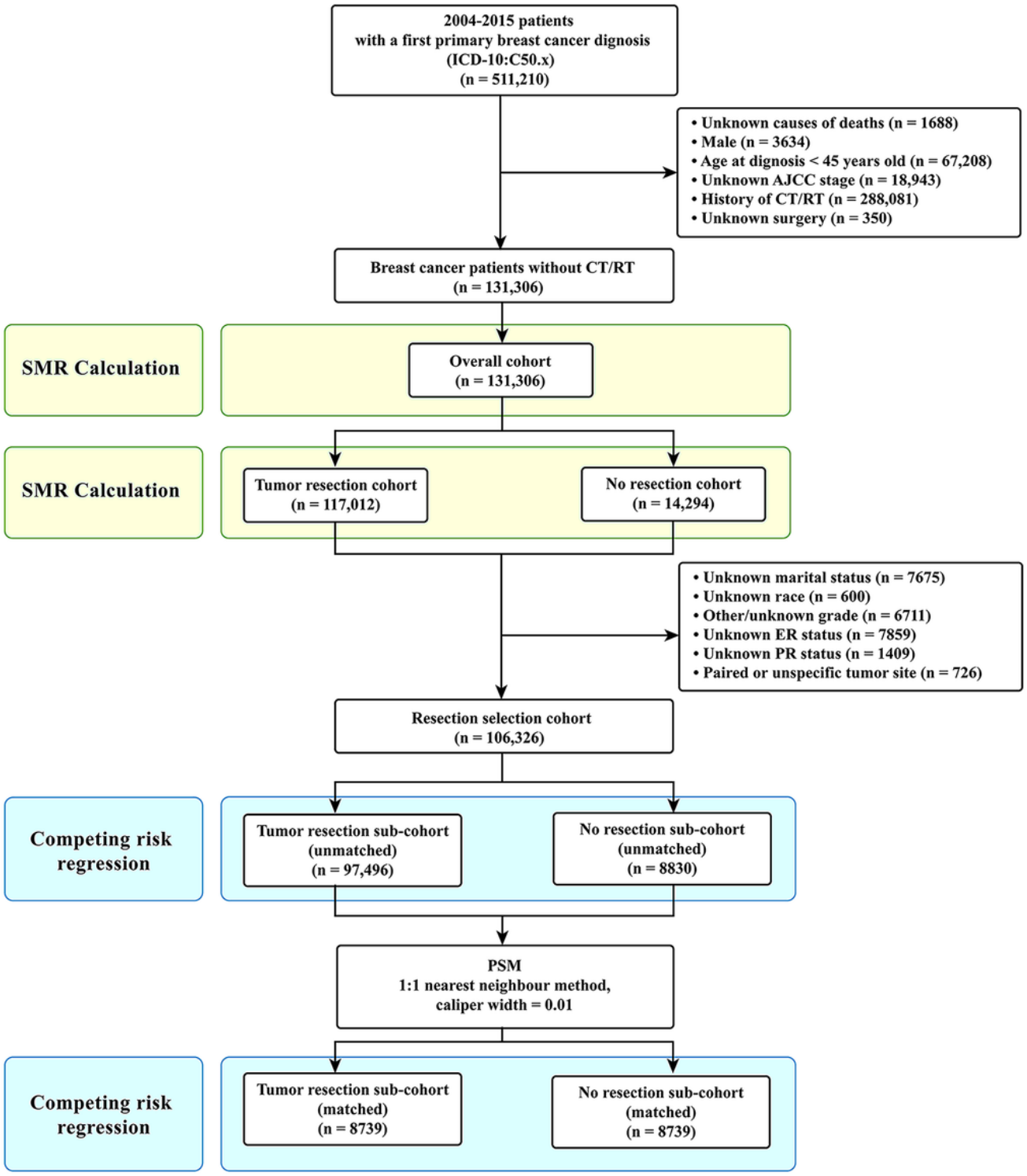

Figure 1

Selection of eligible patients and study design. Abbreviations: CVD, cardiovascular death; SMR, standardized mortality ratio.

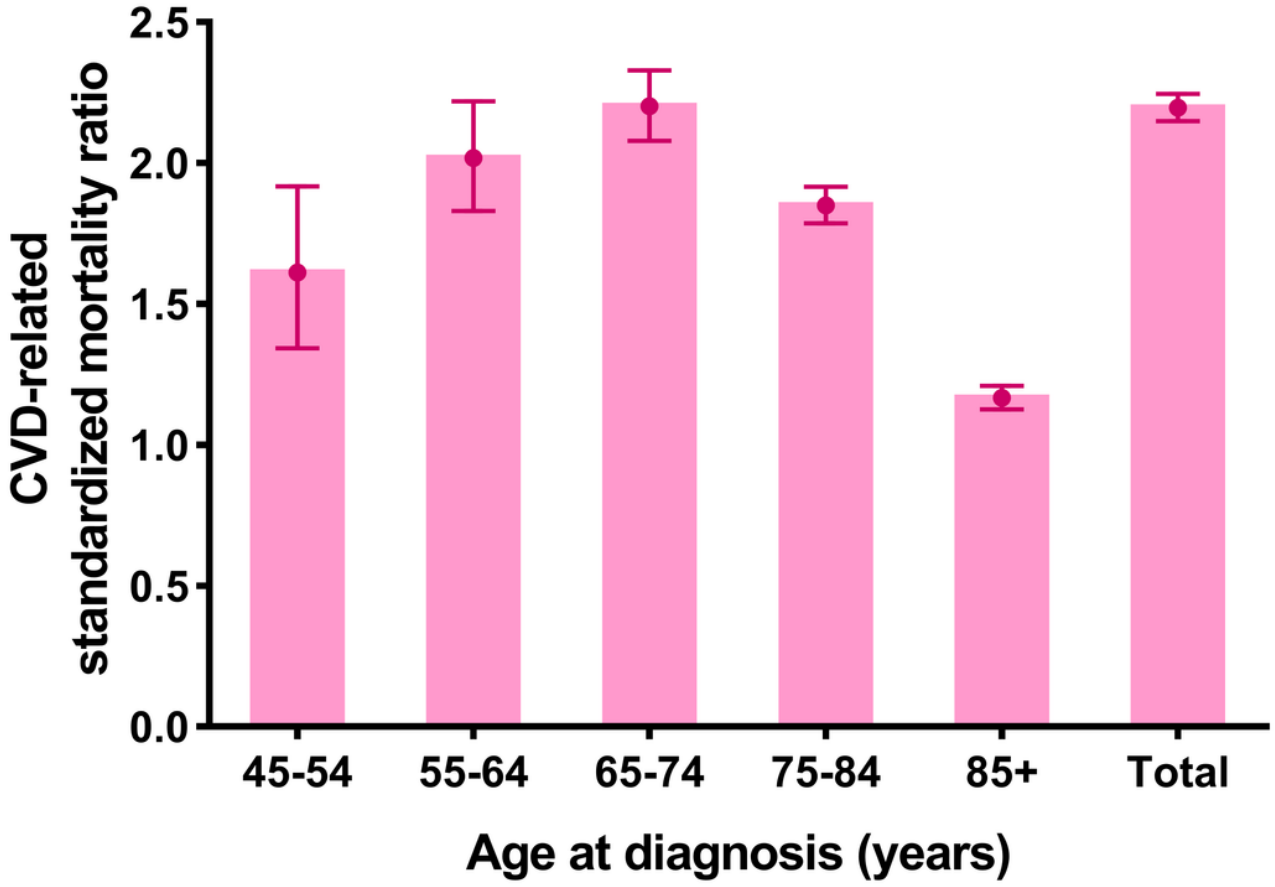

Figure 2

CVD-related SMRs for breast cancer patients without chemotherapy or radiotherapy.

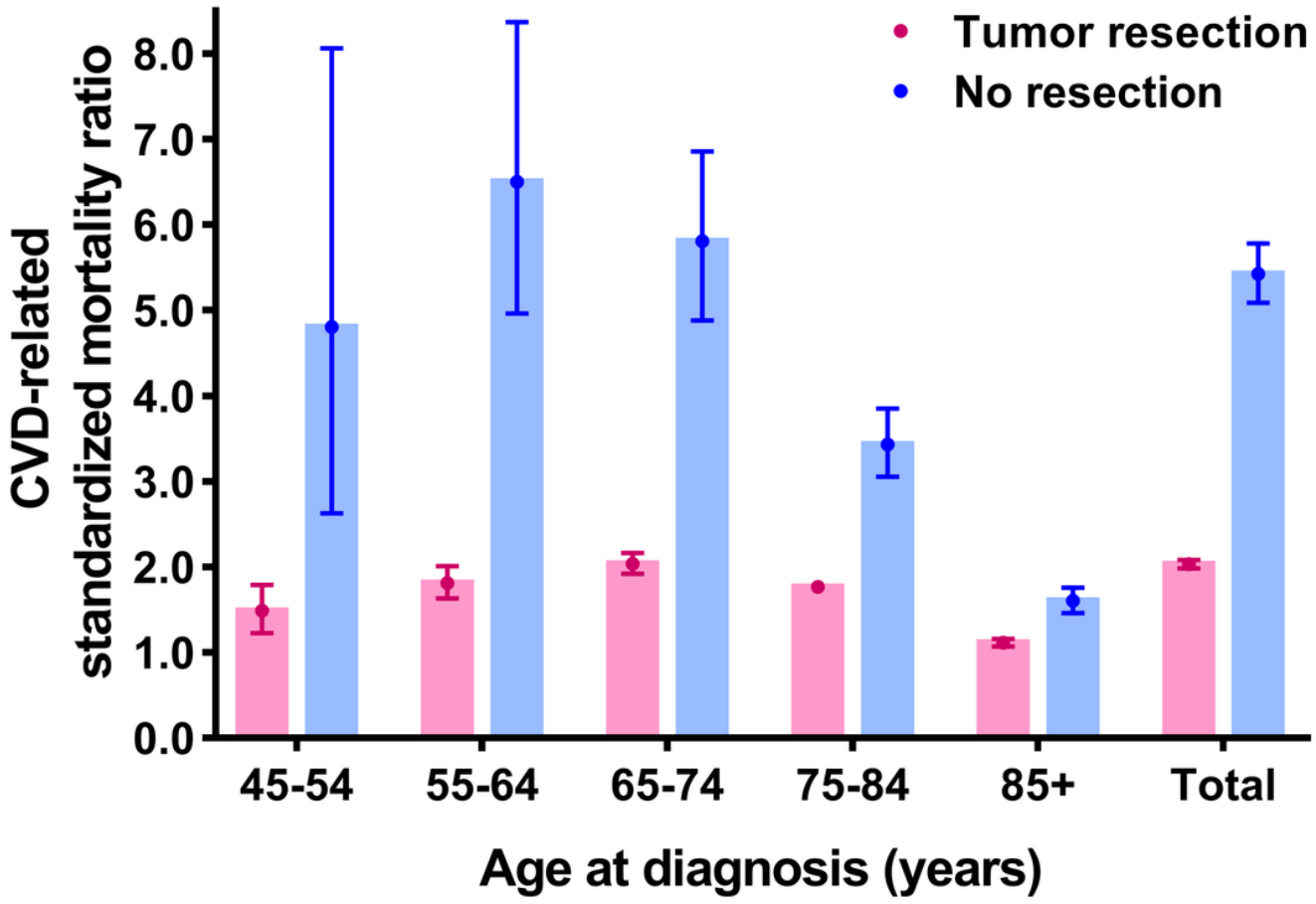

Figure 3

CVD-related SMRs for breast cancer patients with and without tumor resection.

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