Association of marital status with cardiovascular outcome in patients with breast cancer

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Background: The influences of marital status on cardiovascular death risk in patients with breast cancer remained unclear. This study aimed to evaluate the associations of different marital status with cardiovascular death risk in patients with breast cancer.

Methods: A total of 182,666 female breast cancer patients were enrolled in this study from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2014, and was divided into two groups: married (N=107,043) and unmarried (N=75,623). A 1:1 propensity score matching (PSM) was applied to reduce inter-group bias between the two groups. Competing-risks model was used to assess the associations between different marital status and cardiovascular death risk in patients with breast cancer.

Results: After PSM, marital status was an independent predictor for cardiovascular death in patients with breast cancer. Unmarried condition was associated with increased cardiovascular death risk than married condition among breast cancer patients [unadjusted model: hazard ratio (HR) =2.012, 95% confidence interval (CI): 1.835–2.208, P<0.001; Model 1: HR =1.958, 95% CI: 1.785–2.148, P<0.001; Model 2: HR =1.954, 95% CI: 1.781–2.144, P<0.001; Model 3: HR =1.920, 95% CI: 1.748–2.107, P<0.001]. With the exception of separated condition (adjusted HR =0.886, 95% CI: 0.474–1.658, P=0.705), further unmarried subgroups analysis showed that the other three unmarried status were associated with increased cardiovascular death risk as follows: single (adjusted HR =1.623, 95% CI: 1.421–1.853, P<0.001), divorced (adjusted HR =1.394, 95% CI: 1.209–1.608, P<0.001), and widowed (adjusted HR =2.460, 95% CI: 2.227–2.717, P<0.001). In particularly, widowed condition showed the highest cardiovascular death risk in all 4 unmarried subgroups.

Conclusions: Unmarried condition (e.g., single, divorced and widowed) was associated with elevated cardiovascular death risk compared with their married counterparts in patients with breast cancer, suggesting that more attention and humanistic care should be paid to unmarried breast cancer patients (especially the widowed patients) in the management of female breast cancer patients.

Keywords: Breast cancer; cardiovascular death; marital status; Surveillance, Epidemiology, and End Results (SEER); cardio-oncology

Introduction

Breast cancer is the most common carcinoma among women, accounting for approximately 24.2% of all female cancer cases, which has become the leading cause of cancer death in female patients (1). Death causes of breast cancer patients include cancer-related causes and non-cancer-related causes. Cardiovascular death, as the major cause of non-cancer-related morbidities, serves as the major contribution to mortality in patients with breast cancer (2), indicating that the prevention and control of cardiovascular death may contribute to the survival improvement in breast cancer patients. The risk factor identification of cardiovascular death is one of important strategies to prevent cardiovascular death in patients with breast cancer.

Previous studies mostly focused on the relationship between anticancer treatment and cardiovascular death in breast cancer patients (3-5). Besides cardiovascular death risk originating from anti-tumor therapy, social and psychological factors were emphasized in cardio-oncology (6,7). Marital status is one of ignored but important social and psychological factors (8), however, the relationship between marital status and cardiovascular death in breast cancer patients was still unknown. Marital status was evidently relevant to overall survival and cancer-caused special survival in cancer patients (9,10). Married status was related to lower cardiovascular events risk in general population (8,11), and married patients had lower risk of adverse cardiovascular events (12). These findings suggested marital status was playing a significant role in cardiovascular diseases in patients with breast cancer. Furthermore, previous studies reported that unmarried cancer patients were at a higher risk of stroke related death (6) and disease-specific mortality (7). However, these studies only provided limited evidence because of the limited types of unknown marital status and univariate analyses (6,7). The influence of different marital status (e.g., married, single, separation, divorce and widow) on cardiovascular death in breast cancer patients remained unclear. Hence, the present population-based, propensity-matched study was conducted to arrest the association between marital status and cardiovascular death risk, and to further explore the impact of different marital status

on cardiovascular death in patients with breast cancer based on the Surveillance, Epidemiology, and End Results (SEER) database. We presented the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1261/rc).

Methods

The source of data

We extracted the data from the SEER*Stat software (version 8.3.6) with access to the SEER database, an authoritative shared database in the U.S., which had been widely used for cardio-oncology studies. Publicly available information in SEER did not require ethical approval. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study population and design

The female patients with pathological diagnosis of breast cancer were identified in the SEER database from 2010 to 2014. The patients were selected if meeting the following criteria: (I) case selection (site and morphology, primary site-labeled) being 'C50.x'; (II) age at diagnosis greater than or equal to 25 years; (III) known marital status; (IV) female; (V) clear cause of death. The exclusion criteria were as follows: (I) without pathological diagnosis; (II) individuals with multiple primary tumors; (III) either autopsy only or death certificate only; (IV) missing race record; (V) unclear grade; (VI) unclear stage [breast cancer Adjusted the American Joint Committee on Cancer (AJCC) staging system stage Cancer Staging Manual 6th Edition]; (VII) unknown estrogen receptor (ER) status or progesterone receptor (PR) status or human epidermal receptor 2 (HER2) status. A total of 182,666 breast cancer patients were divided into two groups: married (legal marriage) and unmarried (single, separated, divorced, widowed and domestic partners) (9), which were used to explore the association of marital status with cardiovascular death in breast cancer patients. Domestic partners were then excluded due to small sample size (N=493). In

total, 182,173 breast cancer patients were classified as five subgroups as follows: married (N=107,043), single (N=28,246), separated (N=2070), divorced (N=20,656) and widowed (N=24,158). We further quantitatively evaluated the impact of different marital status on cardiovascular death in breast cancer patients. Categorical variables included marital status (married and unmarried), age at diagnosis (25–60 and >60 years) (13), race (white, black and other), income (low and high) (14), grade (low and high), ER status (positive and negative), PR status (positive and negative), HER2 status (positive and negative), AJCC stage (I, II, III and IV), surgery (yes and no evidence), chemotherapy (yes and no evidence) and radiotherapy (yes and no evidence). As for the income, low household income represented the worst 50% among all breast cancer patients, and high household income represented the best 50% among all breast cancer patients (14). Low grade included well differentiated (Grade I) and moderately differentiated (Grade II), while high grade included poorly differentiated (Grade III) and undifferentiated (Grade IV).

Propensity score matching (PSM)

A 1:1 PSM was utilized to balance the bias between the married and unmarried groups referring to our previous project (15,16). Logistic regression was used to estimate propensity scores. The nearest neighbor algorithm with caliper width of 0.02 was applied to perform matching. All the variables in the baseline were enrolled into the propensity score calculation. When the P values were higher than 0.05, we considered that the two groups reached a balance.

Study endpoint

The primary endpoint was cardiovascular death. According to the International Classification of Diseases-10 (ICD-10) codes (17), it was defined as death attributable to cardiovascular diseases including disease of heart, atherosclerosis, cerebrovascular disease, aortic aneurysm and dissection, other diseases of arteries, arterioles and capillaries, and hypertension without heart disease. The follow-up time was counted as the period from first diagnosis with breast cancer to the date of death or last follow-up. The deadline date was December 31, 2015.

Statistical analysis

The statistical analyses were conducted by SPSS version 25.0 (SPSS, Chicago, IL, USA), R software version 3.6.1, and Stata version 15 (StataCorp, College Station, USA). Categorical variables were presented as frequencies. χ^2 test was used to analyze the associations between marital status and these categorical variables at baseline. Given that non-cardiovascular death was a competing risk, univariate competing-risks models were applied to evaluate the relationship between marital status (married and unmarried) and cardiovascular death risk in patients with breast cancer. Multivariate competing-risks regression analyses were further performed to avoid false-positive results (18). Further subgroup analyses were used to evaluate the associations between different marital status (married, single, separated, divorced and widowed) and cardiovascular death risk in patients with breast cancer. Statistical significance was defined by a two-tailed P value less than 0.05.

Results

Baseline characteristic in study participants

As shown in *Table 1*, a total of 182,666 patients with breast cancer were enrolled to present study before PSM. There were significant differences on age at diagnosis (P<0.001), race (P<0.001), income (P<0.001), grade (P<0.001), ER status (P<0.001), PR status (P<0.001), HER2 status (P=0.001), AJCC stage (P<0.001), surgery (P<0.001), chemotherapy (P<0.001) and radiotherapy (P<0.001) between the two groups. After PSM, 141,302 breast cancer patients were eventually identified. There were no significant differences on the above-mentioned variables between the two groups, except race (P<0.001), surgery (P=0.014), PR status (P=0.008) and ER status (P=0.028), whereas PR status and ER status were not related to the cardiovascular death risk in patients with breast cancer (Table S1).

Association of marital status with cardiovascular death risk in patients with breast cancer

Before PSM, unmarried condition was associated with increased cardiovascular death risk [unadjusted hazard ratio (HR) =3.085, 95% confidence interval (CI): 2.831–3.361, P<0.001] compared to their married counterparts in patients with breast cancer, as shown in *Figure 1A*, *Table 2*, and Table S1. To correct for confounding bias, multivariate analysis further demonstrated that marital status was an independent predictor for cardiovascular death in

Table 1 Baseline characteristics before and after PSM

Variables	Before PSM, N (%)			After PSM, N (%)		
	Married	Unmarried	P	Married	Unmarried	P
N	107,043	75,623		70,651	70,651	
Age at diagnosis			<0.001			0.970
25–60 years	61,453 (57.4)	33,290 (44.0)		33,073 (46.8)	33,066 (46.8)	
>60 years	45,590 (42.6)	42,333 (56.0)		37,578 (53.2)	37,585 (53.2)	
Race			<0.001			<0.001
White	87,807 (82.0)	57,037 (75.4)		56,836 (80.4)	53,779 (76.1)	
Black	7,486 (7.0)	12,841 (17.0)		11,601 (16.4)	5,515 (7.8)	
Other&	11,750 (11.0)	5745 (7.6)		5,271 (7.5)	8,300 (11.7)	
Income*			<0.001			0.412
Low	51,709 (48.3)	40,042 (52.9)		36,413 (51.5)	36,567 (51.8)	
High	55,334 (51.7)	35,581 (47.1)		34,238 (48.5)	34,084 (48.2)	
Grade#			<0.001			0.096
Low	71,224 (66.5)	48,979 (64.8)		46,318 (65.6)	46,020 (65.1)	
High	35,819 (33.5)	26,644 (35.2)		24,333 (34.4)	24,631 (34.9)	
ER status			<0.001			0.028
Positive	88,774 (82.9)	61,909 (81.9)		58,061 (82.2)	57,744 (81.7)	
Negative	18,269 (17.1)	13,714 (18.1)		12,590 (17.8)	12,907 (18.3)	
PR status			<0.001			0.008
Positive	78,232 (73.1)	53,786 (71.1)		50,822 (71.9)	50,373 (71.3)	
Negative	28,811 (26.9)	21,837 (28.9)		19,829 (28.1)	20,278 (28.7)	
HER2 status			0.001			0.441
Positive	16,813 (15.7)	11,464 (15.2)		10,808 (15.3)	10,704 (15.2)	
Negative	90,230 (84.3)	64,159 (84.8)		59,843 (84.7)	59,947 (84.8)	
AJCC stage			<0.001			0.136
I	55,868 (52.2)	35,212 (46.6)		34,673 (49.1)	34,462 (48.8)	
II	35,919 (33.6)	26,335 (34.8)		24,414 (34.2)	24,136 (34.2)	
III	11,504 (10.7)	9,693 (12.8)		8,383 (11.9)	8,658 (12.3)	
IV	3,752 (3.5)	4,383 (5.8)		3,451 (4.9)	3,395 (4.8)	
Surgery			<0.001			0.014
Yes	102,342 (95.6)	69,275 (91.6)		66,210 (93.7)	66,453 (94.1)	
No evidence	4,701 (4.0)	6,348 (8.4)		4,441 (6.3)	4198 (5.9)	
Chemotherapy			<0.001			0.833
Yes	58,144 (54.3)	45,706 (60.4)		41,304 (58.5)	41,265 (58.4)	
No evidence	48,899 (45.7)	29,917 (39.6)		29,347 (41.5)	29,386 (41.6)	
Radiotherapy			<0.001			0.953
Yes	47,017 (43.9)	38,047 (50.3)		34,066 (48.2)	34,055 (48.2)	
No evidence	60,026 (56.1)	37,576 (49.7)		36,585 (51.8)	36,596 (51.8)	

&, other includes American Indian/Alaska Native and Asian/Pacific Islander; *, low (median household income was the worst 50% among all breast cancer patients) and high (median household income was the best 50%); #, low (Grade I: well-differentiated and Grade II: moderately differentiated) and high (Grade III: poorly differentiated and Grade IV: undifferentiated). PSM, propensity-score matching; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal receptor 2; AJCC, the American Joint Committee on Cancer.
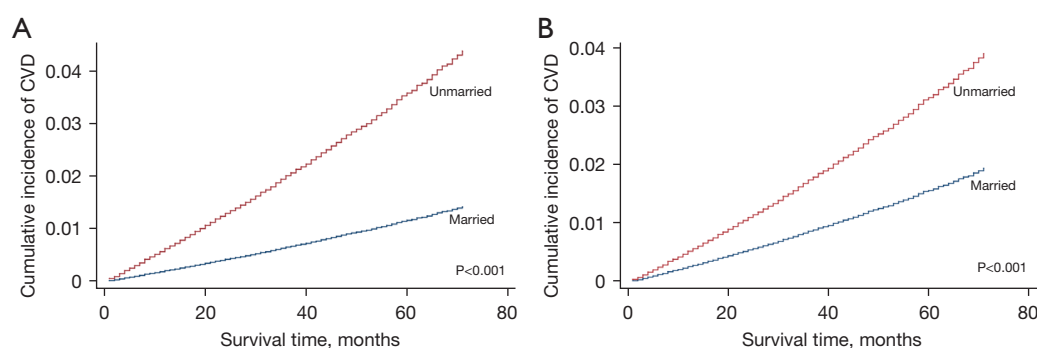
Figure 1 Cumulative incidence of cardiovascular death in marital status. (A) Univariate competing-risks regression analysis of cardiovascular death before PSM; (B) univariate competing-risks regression analysis of cardiovascular death after PSM. CVD, cardiovascular disease death; PSM, propensity score matching.

Table 2 Multivariate competing-risks regression analysis of cardiovascular death

Variables	Before PSM		After PSM	
	HR (95% CI)	P value	HR (95% CI)	P value
Unadjusted HR				
Married	Reference		Reference	
Unmarried	3.085 (2.831–3.361)	<0.001	2.012 (1.835–2.208)	<0.001
Model 1[a]				
Married	Reference		Reference	
Unmarried	2.043 (1.871–2.230)	<0.001	1.958 (1.785–2.148)	<0.001
Model 2[b]				
Married	Reference		Reference	
Unmarried	2.039 (1.867–2.226)	<0.001	1.954 (1.781–2.144)	<0.001
Model 3[c]				
Married	Reference		Reference	
Unmarried	1.971 (1.802–2.155)	<0.001	1.920 (1.748–2.107)	<0.001

[a], Model 1: HR was adjusted for statistically significant factors according to univariate analysis (age at diagnosis, income, grade, HER2 status, AJCC stage, chemotherapy and radiotherapy); [b], Model 2: it was the same as Model 1, and also included ER status and PR status; [c], Model 3: It is the same as Model 2, and also includes race and surgery. PSM, propensity-score matching; HR, hazard ratio; CI, confidence interval; HER2, human epidermal receptor 2; AJCC, the American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor.

breast cancer patients, as shown in *Table 2*. Adjustment for confounding covariates (Model 1: all covariates in the baseline) showed that unmarried condition was still associated with increased cardiovascular death risk (HR =2.043, 95% CI: 1.871–2.230, P<0.001). After adjustment (Model 2: it was same as Model 1, and also including ER status and PR status; Model 3: it was the same as Model 2, and also included race and surgery), it indicated a robust

adjusted HR on cardiovascular death risk (Model 2: HR =2.039, 95% CI: 1.867–2.226, P<0.001; Model 3: HR =1.971, 95% CI: 1.802–2.155, P<0.001)

After PSM, similar phenomenon was observed, and unmarried breast cancer patients still had higher cardiovascular death risk in unadjusted model: HR =2.012, 95% CI: 1.835–2.208, P<0.001), Model 1 (HR =1.958, 95% CI: 1.785–2.148, P<0.001), Model 2 (HR =1.954, 95% CI:

Table 3 Univariate and multivariate competing-risks regression analysis base on different marital status of 182,173 patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)*	P value
Marital status				
Married	Reference		Reference	
Single	1.617 (1.420–1.842)	<0.001	1.623 (1.421–1.853)	<0.001
Separated	0.711 (0.381–1.327)	0.284	0.886 (0.474–1.658)	0.705
Divorced	1.712 (1.486–1.973)	<0.001	1.394 (1.209–1.608)	<0.001
Widowed	6.208 (5.658–6.811)	<0.001	2.460 (2.227–2.717)	<0.001

*, HR was adjusted for statistically significant factors according to univariate analysis (age at diagnosis, race, income, grade, HER2 status, AJCC stage, surgery, chemotherapy and radiotherapy). HR, hazard ratio; CI, confidence interval; HER2, human epidermal receptor 2; AJCC, the American Joint Committee on Cancer.
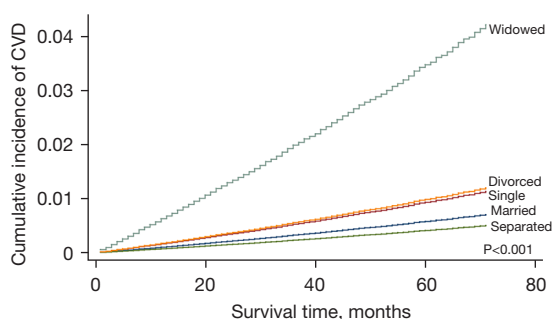
Figure 2 Cumulative incidence of cardiovascular death in different marital status. CVD, cardiovascular disease death.

1.781–2.144, P<0.001), and Model 3 (HR =1.920, 95% CI: 1.748–2.107, P<0.001), as shown in *Figure 1B*, *Table 2*, and Tables S1-S4.

Association of different marital status with cardiovascular death risk in patients with breast cancer

As shown in *Table 3*, the separated condition was not correlated with cardiovascular death risk before PSM (HR =0.711, 95% CI: 0.381–1.327, P=0.284) and after PSM (HR =0.886, 95% CI: 0.474–1.658, P=0.705). With the exception of separated condition, the other three unmarried conditions were linked to higher cardiovascular death risk as follows: single (adjusted HR =1.623, 95% CI: 1.421–1.853, P<0.001), divorced (adjusted HR =1.394, 95% CI: 1.209–1.608, P<0.001), and widowed (adjusted HR =2.460, 95% CI: 2.227–2.717, P<0.001) (*Table 3* and Table S5). In particularly, widowed condition had the highest cardiovascular death risk in all 4 unmarried subgroups (*Figure 2*, *Table 3* and Table S5).

Discussion

Marriage, one of the important social and psychological factors, has been proven closely related with the cardiovascular prognosis of patients with cancer. Breast cancer is one of the mostly common forms of cancer worldwide. The association of marital status (married *vs.* unmarried) with cardiovascular death risk of patients with breast cancer is still ambiguous. Previous studies found that marital status was associated with cardiovascular death risk of patients with breast cancer, and unmarried patients suffered from higher cardiovascular death risk. However, these findings may be confounded by three factors as follows: firstly, unlike the various classifications of marital status, the limited type of "unknown marital status" may limit their results. Secondly, these studies were restricted to univariate analysis and could not exclude possible false-positive data. Lastly, these studies neglected the competing risk of non-cardiovascular death. Hence, by reducing inter-group bias via PSM and correcting for potential confounding factors with multivariate competitive risk model analysis, the present study found that unmarried condition was obviously associated with increased cardiovascular death risk (approximately by 1-fold) in patients with breast cancer. It was partially consistent with a prospective cohort study by Schultz *et al.* (8), who reported that the cardiovascular mortality risk in 1,963 unmarried patients increased by 24%, a observational study by Zaorsky *et al.* who found that the stroke death risk of 2,895,946 unmarried cancer patients also increased by 1.15-fold (6), and an investigation by Stoltzfus *et al.* who reported that the risk of fatal heart disease in 2,895,946 unmarried cancer patients increased by 1.23-fold (7). Similarly, Onwudiwe

et al. (19) further confirmed that cardiovascular event-free survival in 30,239 unmarried patients with breast cancer raised by 1.22-fold after adjusting baseline cardiovascular risk factors.

As far as the cardiovascular benefit of marriage was concerned, it was owing to social and emotional support, especially spousal support (11,20) and supervision (21,22). Firstly, spousal support and supervision promoted healthy lifestyle changes (defined as primary prevention of cardiovascular disease) for breast cancer survivors (21,22). Since being diagnosed with breast cancer, married female was more likely to cultivate a healthy lifestyle due to the supervision of spouse. Conversely, unmarried breast cancer patients, who lacked the support and care from spouse, were more likely to suffer from psychological distress and become addicted to bad lifestyle (e.g., smoking and excessive drinking) (23-26). Secondly, supervision and care of spouse usually promoted early detection, early diagnosis and early treatment (defined as secondary prevention of cardiovascular disease for breast cancer survivors) (11,20). Support from spouse improved adherence to treatments in breast cancer patients with cardiovascular complications, while unmarried ones were possibly non-adherent to their prescribed medications, thus related to higher cardiovascular death risk (27).

Besides social and emotional support, other potential explanations might be related to physiological factors. The cancer diagnosis brought out varying degrees of psychological stress, such as cancer-related distress, depression and anxiety, which were considered as risk factors increasing the cardiovascular death risk in breast cancer patients (28,29). The married breast cancer patients suffered from less psychological burden, because the spouse shared the burden of negative emotions and offered positive emotional support (30). Unmarried patients may tend to suffer more negative emotions. Physiological factors (e.g., perceived stress and chronicity of stress) mediated the harmful influence of marital status on cardiovascular events among breast cancer patients via higher oxidative stress, lower telomerase activity, and shorter telomere length (31). Oxidative stress and shortened telomeres might result in higher rate of cardiovascular death in unmarried patients. A Swedish population-based cohort study reported that single individuals had a shorter leucocyte telomere length (a biomarker of aging) and higher risk of cardiovascular diseases than married individuals (32). In addition, increased level of cortisol was related to poorer cardiovascular outcomes. Unmarried patients had higher cortisol levels than married patients (33), which induced cardiac dysfunction (34) and further increases the risk of cardiovascular disease (35).

What's more important, the present study is the first to evaluate the associations of different unmarried conditions with cardiovascular death risk in unmarried patients with breast cancer. Unmarried patients with breast cancer had elevated cardiovascular death risk, but the harmful effect was heterogeneous with different unmarried conditions. According to marriage history, unmarried breast cancer patients were divided into two subgroups as follows: those without marriage history (e.g., single) and those with marriage history (e.g., widowed and divorced). The cardiovascular death risk in unmarried breast cancer patients without marriage history (e.g., single) was increased by 60% compared to their married counterparts. Among the unmarried breast cancer patients with marriage history, the risk under widowed circumstances was much worse (increased by 50%) than singled while slightly lower (decreased by 15%) in divorced. Our findings were partially consistent with the Japanese prospective cohort study by Tanno *et al.* (36) who reported that single, divorced, or widowed hemodialysis patients were all at greater cardiovascular death risk than married patients, and the investigation by Otto *et al.* who found that single, divorced or widowed patients had higher risk of cardiovascular disease and its related death, compared with married individuals (37). Possible potential explanations may be owed to psychological stress under different unmarried status. Subjects with single, divorced and widowed had a tendency of diagnosis with a chronic stress syndrome (38), but the stress status was manifested with heterogeneity based on different unmarried conditions (30). Chronic exposure to stressors caused endocrine and immune system dysfunction that contributed to sustained low-grade inflammation (39). Growing evidence demonstrated that different unmarried status were linked to varying degrees of low-grade inflammation (40,41). It is well-known that low-grade systemic chronic inflammation acts the essential role in occurrence and development of cardiovascular events. Indeed, the highest cardiovascular death risk was found in widowed breast cancer patients. The loss of spouse could render "broken heart" which leaded to lower heart rate variability and higher pro-inflammatory cytokine levels, further putting patients at high cardiovascular death risk (42). These findings suggested that regular test of high-sensitivity C-reactive protein level could be one of the significant strategies to improve cardiovascular prognosis in breast cancer patients with different unmarried conditions.

Strengths and limitations

The strengths in this study were the large sample size and long follow-up time. It was the first population-based study to show the association between marital status and cardiovascular death risk in patients with breast cancer. Some limitations of this study need to be mentioned. Firstly, marital status was only registered at the time of diagnosis of breast cancer in SEER database, and we were unable to further explore the impact of marriage change on cardiovascular death in breast cancer patients. Secondly, the quality of marriage was also unavailable in SEER database, and we could not further investigate the effect of marriage quality on cardiovascular death risk in breast cancer patients. Thirdly, there is a possibility that married women may be physically, psychologically or emotionally healthier than those who were unmarried, which may increase selection bias. Finally, the SEER registries did not provide information about comorbidities and previous medical history. Though we balanced the variables at baseline levels, there might be unobserved variables that might affect study outcomes, such as comorbidities and previous medical history. Similar to the previous SEER-based cardio-oncology studies (6,7,43,44), our study couldn't further explore the contribution of marital status on cardiovascular death of breast cancer patients after adjusting comorbidities and previous medical history.

Conclusions

Unmarried breast cancer patients (e.g., single, divorced and widowed) were associated with higher cardiovascular death risk compared with married patients, suggesting that more attention and humanistic care should be offered to unmarried patients in the management of female breast cancer patients, especially to those widowed patients.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1261/rc

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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).

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Table S1 Univariate competing-risks regression analysis of cardiovascular death

Variable	Before PSM		After PSM	
	HR (95% CI)	P value	HR (95% CI)	P value
Marital status				
Married	Reference		Reference	
Unmarried	3.085 (2.831–3.361)	<0.001	2.012 (1.835–2.208)	<0.001
Age at diagnosis				
25–60 years	Reference		Reference	
>60 years	11.176 (9.715–12.856)	<0.001	9.382 (8.035–10.956)	<0.001
Race				
White	Reference		Reference	
Black	1.136 (1.009–1.279)	0.035	0.950 (0.831–1.086)	0.455
Other[&]	0.504 (0.418–0.608)	<0.001	0.492 (0.401–0.604)	<0.001
Income[*]				
Low	Reference		Reference	
High	0.748 (0.690–0.811)	<0.001	0.831 (0.762–0.908)	<0.001
Grade[#]				
Low	Reference		Reference	
High	0.918 (0.843–1.000)	0.049	0.860 (0.783–0.945)	0.002
ER status				
Positive	Reference		Reference	
Negative	0.946 (0.851–1.053)	0.309	0.947 (0.844–1.063)	0.354
PR status				
Positive	Reference		Reference	
Negative	0.979 (0.895–1.070)	0.634	0.965 (0.876–1.063)	0.469
HER2 status				
Positive	Reference		Reference	
Negative	1.270 (1.125–1.433)	<0.001	1.258 (1.101–1.436)	0.001
AJCC stage				
I	Reference		Reference	
II	1.390 (1.272–1.518)	<0.001	1.236 (1.123–1.361)	<0.001
III	1.369 (1.208–1.550)	<0.001	1.126 (0.980–1.294)	0.095
IV	1.446 (1.201–1.741)	<0.001	1.135 (0.921–1.399)	0.236
Surgery				
Yes	0.357 (0.318–0.401)	<0.001	0.550 (0.473–0.638)	<0.001
No evidence	Reference		Reference	
Chemotherapy				
Yes	0.245 (0.220–0.273)	<0.001	0.271 (0.241–0.305)	<0.001
No evidence	Reference		Reference	
Radiotherapy				
Yes	0.332 (0.304–0.363)	<0.001	0.370 (0.337–0.407)	<0.001
No evidence	Reference		Reference	

[&], other includes American Indian/Alaska Native and Asian/Pacific Islander; [*], low (median household income was the worst 50% among all breast cancer patients) and high (median household income was the best 50%); [#], low (Grade I: well-differentiated and Grade II: moderately differentiated) and high (Grade III: poorly differentiated and Grade IV: undifferentiated). PSM, propensity-score matching; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal receptor 2; AJCC, the American Joint Committee on Cancer.

Table S2 Multivariate competing-risks regression analysis of cardiovascular death (Model 1)

Variable	Before PSM		After PSM	
	HR (95% CI)	P value	HR (95% CI)	P value
Marital status				
Married	Reference		Reference	
Unmarried	2.043 (1.871–2.230)	<0.001	1.958 (1.785–2.148)	<0.001
Age at diagnosis				
25–60 years	Reference		Reference	
>60 years	7.742 (6.723–8.914)	<0.001	7.634 (6.537–8.914)	<0.001
Income*				
Low	Reference		Reference	
High	0.855 (0.789–0.928)	<0.001	0.848 (0.777–0.926)	<0.001
Grade#				
Low	Reference		Reference	
High	1.191 (1.084–1.309)	<0.001	1.182 (1.066–1.311)	0.002
HER2 status				
Positive	Reference		Reference	
Negative	0.923 (0.811–1.051)	0.227	0.873 (0.757–1.005)	0.060
AJCC stage				
I	Reference		Reference	
II	1.695 (1.545–1.859)	<0.001	1.685 (1.524–1.862)	<0.001
III	2.235 (1.957–2.553)	<0.001	2.406 (2.073–2.792)	<0.001
IV	1.471 (1.216–1.779)	<0.001	1.584 (1.279–1.960)	<0.001
Chemotherapy				
Yes	0.341 (0.304–0.382)	<0.001	0.321 (0.282–0.365)	<0.001
No evidence	Reference		Reference	
Radiotherapy				
Yes	0.422 (0.386–0.462)	<0.001	0.424 (0.385–0.468)	<0.001
No evidence	Reference		Reference	

*, low (median household income was the worst 50% among all breast cancer patients) and high (median household income was the best 50%); #, low (Grade I: well-differentiated and Grade II: moderately differentiated) and high (Grade III: poorly differentiated and Grade IV: undifferentiated). PSM, propensity-score matching; HR, hazard ratio; CI, confidence interval; HER2, human epidermal receptor 2; AJCC, the American Joint Committee on Cancer.

Table S3 Multivariate competing-risks regression analysis of cardiovascular death (Model 2)

Variable	Before PSM		After PSM	
	HR (95% CI)	P value	HR (95% CI)	P value
Marital status				
Married	Reference		Reference	
Unmarried	2.039 (1.867–2.226)	<0.001	1.954 (1.781–2.144)	<0.001
Age at diagnosis				
25–60 years	Reference		Reference	
>60 years	7.732 (6.715–8.905)	<0.001	7.618 (6.523–8.961)	<0.001
Income*				
Low	Reference		Reference	
High	0.857 (0.791–0.930)	<0.001	0.849 (0.778–0.927)	<0.001
Grade#				
Low	Reference		Reference	
High	1.126 (1.017–1.248)	0.022	1.100 (0.984–1.229)	0.094
ER status				
Positive	Reference		Reference	
Negative	1.228 (1.055–1.428)	0.008	1.277 (1.085–1.503)	0.003
PR status				
Positive			Reference	
Negative	0.985 (0.871–1.113)	0.803	1.011 (0.883–1.157)	0.874
HER2 status				
Positive	Reference		Reference	
Negative	0.941 (0.825–1.072)	0.360	0.895 (0.775–1.033)	0.128
AJCC stage				
I	Reference		Reference	
II	1.698 (1.548–1.863)	<0.001	1.687 (1.525–1.865)	<0.001
III	2.241 (1.962–2.560)	<0.001	2.406 (2.074–2.791)	<0.001
IV	1.474 (1.218–1.783)	<0.001	1.589 (1.284–1.967)	<0.001
Chemotherapy				
Yes	0.333 (0.296–0.374)	<0.001	0.310 (0.272–0.353)	<0.001
No evidence	Reference		Reference	
Radiotherapy				
Yes	0.424 (0.388–0.465)	<0.001	0.428 (0.388–0.472)	<0.001
No evidence	Reference		Reference	

*, low (median household income was the worst 50% among all breast cancer patients) and high (median household income was the best 50%); #, low (Grade I: well-differentiated and Grade II: moderately differentiated) and high (Grade III: poorly differentiated and Grade IV: undifferentiated). PSM, propensity-score matching; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal receptor 2; AJCC, the American Joint Committee on Cancer.

Table S4 Multivariate competing-risks regression analysis of cardiovascular death (Model 3)

Variable	Before PSM		After PSM	
	HR (95% CI)	P value	HR (95% CI)	P value
Marital status				
Married	Reference		Reference	
Unmarried	1.971 (1.802–2.155)	<0.001	1.920 (1.748–2.107)	<0.001
Age at diagnosis				
25–60 years	Reference		Reference	
>60 years	7.662 (6.656–8.821)	<0.001	7.692 (6.588–8.980)	<0.001
Race				
White	Reference		Reference	
Black	1.089 (0.963–1.230)	0.173	1.168 (1.020–1.338)	0.024
Other[&]	0.645 (0.534–0.778)	<0.001	0.649 (0.528–0.797)	<0.001
Income*				
Low	Reference		Reference	
High	0.873 (0.804–0.947)	0.001	0.872 (0.798–0.953)	0.002
Grade[#]				
Low	Reference		Reference	
High	1.134 (1.024–1.256)	0.016	1.102 (0.986–1.231)	0.086
ER status				
Positive	Reference		Reference	
Negative	1.221 (1.050–1.421)	0.010	1.255 (1.066–1.478)	0.006
PR status				
Positive	Reference		Reference	
Negative	0.980 (0.866–1.107)	0.742	1.001 (0.875–1.145)	0.990
HER2 status				
Positive	Reference		Reference	
Negative	0.944 (0.828–1.076)	0.388	0.914 (0.792–1.054)	0.216
AJCC stage				
I	Reference		Reference	
II	1.652 (1.505–1.813)	<0.001	1.659 (1.500–1.835)	<0.001
III	2.070 (1.806–2.373)	<0.001	2.252 (1.936–2.620)	<0.001
IV	1.001 (0.803–1.250)	0.989	1.101 (0.851–1.426)	0.464
Surgery				
Yes	0.580 (0.503–0.669)	<0.001	0.592 (0.490–0.716)	<0.001
No evidence	Reference		Reference	
Chemotherapy				
Yes	0.340 (0.303–0.382)	<0.001	0.313 (0.275–0.356)	<0.001
No evidence	Reference		Reference	
Radiotherapy				
Yes	0.443 (0.404–0.486)	<0.001	0.437 (0.396–0.482)	<0.001
No evidence	Reference		Reference	

[&], other includes American Indian/Alaska Native and Asian/Pacific Islander; *, low (median household income was the worst 50% among all breast cancer patients) and high (median household income was the best 50%); [#], low (Grade I: well-differentiated and Grade II: moderately differentiated) and high (Grade III: poorly differentiated and Grade IV: undifferentiated). PSM, propensity-score matching; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal receptor 2; AJCC, the American Joint Committee on Cancer.

Table S5 Multivariate competing-risks regression analysis of cardiovascular death base on different marital status of 182,173 patients

Variable	HR (95% CI)	P value
Marital status		
Married	Reference	
Single	1.623 (1.421–1.853)	<0.001
Separated	0.886 (0.474–1.658)	0.705
Divorced	1.394 (1.209–1.608)	<0.001
Widowed	2.460 (2.227–2.717)	<0.001
Age at diagnosis		
25–60 years	Reference	
>60 years	6.776 (5.863–7.831)	<0.001
Race		
White	Reference	
Black	1.149 (1.017–1.298)	0.026
Other[&]	0.642 (0.532–0.774)	<0.001
Income*		
Low	Reference	
High	0.878 (0.809–0.953)	0.002
Grade[#]		
Low	Reference	
High	1.184 (1.078–1.301)	<0.001
HER2 status		
Positive	Reference	
Negative	0.927 (0.815–1.055)	0.252
AJCC stage		
I	Reference	
II	1.621 (1.477–1.780)	<0.001
III	2.013 (1.756–2.307)	<0.001
IV	1.017 (0.816–1.268)	0.878
Surgery		
Yes	0.593 (0.514–0.683)	
No evidence	Reference	<0.001
Chemotherapy		
Yes	0.367 (0.326–0.412)	<0.001
No evidence	Reference	
Radiotherapy		
Yes	0.452 (0.412–0.495)	<0.001
No evidence	Reference	

[&], other includes American Indian/Alaska Native and Asian/Pacific Islander; *, low (median household income was the worst 50% among all breast cancer patients) and high (median household income was the best 50%); [#], low (Grade I: well-differentiated and Grade II: moderately differentiated) and high (Grade III: poorly differentiated and Grade IV: undifferentiated). HR, hazard ratio; CI, confidence interval; HER2, human epidermal receptor 2; AJCC, the American Joint Committee on Cancer.