

Cause-specific mortality in reproductive-age breast cancer patients: A competing risk approach

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ABSTRACT

Background: Breast cancer (BC) is a leading cause of mortality among women, particularly those in the reproductive age (15-49 years).

Objective: This study aims to examine the survival outcomes of female BC patients in reproductive age groups using a competing risk approach, with a focus on identifying significant determinants of BC-specific mortality and mortality due to other causes.

Materials and methods: This study utilized data from the Surveillance, Epidemiology, and End Results (SEER) database. The analysis included women diagnosed with breast cancer within reproductive age groups. The Cumulative Incidence Function (CIF), cause-specific hazard, and Fine-Gray subdistribution hazard models were employed to estimate the impact of potential determinants on BC-specific and other-cause mortality.

Results: A total of 67063 patients were included in the study. The cumulative incidence of breast cancer-specific mortality and other cause mortality at 5 years was 4.8% and 0.95%, respectively. Age at diagnosis, race, tumor stage, and hormone receptor status were significant predictors of breast cancer-specific mortality. The Fine-Gray model revealed that younger age (15-39 years), advanced tumor stage, and negative hormone receptor status were associated with higher hazards for breast cancer mortality ($p < 0.05$).

Conclusion: The study highlights the importance of using a competing risk model to evaluate the cumulative incidence of prognostic factors in breast cancer patients of reproductive age, especially when competing clinical risks are present. These findings can guide personalized treatment strategies based on individual risk profiles.

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer-related mortality among women globally. According to the GLOBOCAN 2020 report, BC accounts for 24.5% of all cancer cases and 15.5% of cancer deaths among women worldwide.¹ Various risk factors such as early menarche, nulliparity, late age at first pregnancy, use of oral contraceptives, and late menopause have been identified as significant markers for BC development in reproductive-age women.²⁻⁴

Classical survival analysis methods, such as Kaplan-Meier survival analysis, the log-rank test, and the Cox proportional hazards model, are well-established for estimating time-to-event data.^{5,6} However, these methods often fall short in clinical scenarios where multiple endpoints, or competing risks, coexist.⁷ Competing risk analysis extends classical survival analysis by accommodating more than one event

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that affects a patient's survival time.⁸ In the context of BC, the primary outcome is often the time to death due to BC, with death from other causes acting as a competing event.

Competing risk models, such as the cause-specific hazard model and the Fine-Gray subdistribution hazard model, are crucial for accurately identifying predictors of an event and predicting its occurrence.^{9,10} The cause-specific hazard model assesses the effect of covariates on the instantaneous risk of an event. In contrast, the subdistribution hazard model evaluates the impact of covariates on the cumulative incidence function, accounting for competing risks.

Reproductive-age women have unique biological and clinical factors that influence BC prognosis, yet studies focusing on this demographic remain limited. This study aims to address the gap in the existing literature by examining cause-specific mortality among reproductive-age women with BC using these competing risk approaches. By identifying significant predictors of BC-specific and other-cause mortality, this work provides insights that may inform tailored treatment strategies and public health initiatives for this vulnerable group.

Materials and methods

Study design and data source

This retrospective cohort study utilized data from the surveillance, epidemiology, and end results (SEER) database (18-registry, November 2020, 2000-2018), which collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the U.S. population. The SEER program provides comprehensive information on patient demographics, tumor characteristics, treatment, and survival outcomes.¹¹

Study population

This study focuses on reproductive-age women (i.e., 15-49 years), based on the World Health Organization's reproductive age classification. This range encompasses critical life stages where hormonal influences, fertility concerns, and unique biological responses to treatment can impact cancer progression and outcomes. Compared to older women, reproductive-age women often face more aggressive tumor subtypes and distinct treatment challenges, underscoring the need for focused research on this group.

Patients with missing data on key variables, such as tumor stage and hormone receptor status, were excluded from the analysis to ensure data integrity. The final study population consisted of 67,063 patients diagnosed between 2010 and 2015 and registered in the SEER database.

Variables

The primary outcome of interest was cause-specific mortality, which was classified into breast cancer-specific mortality and mortality due to other causes (Figure 1). Patient status is established by combining SEER cause-specific death classification and SEER other cause-of-death classification variables. Patients' status was categorized as 0=alive, 1=death due to BC (BC mortality), and 2=death due to other causes (other-cause mortality). Covariates involved in the analysis include age (at first diagnosis), race & origin, SEER summary stage, Tumor staging, breast subtypes, Regional node positive, ER status, PR status, HER2 status, and breast subtypes. Age at diagnosis is categorized into three groups, i.e., 15-29 years, 30-39 years, and 40-49 years, respectively. Tumor stage classified according to the American Joint Committee on Cancer (AJCC) staging system.

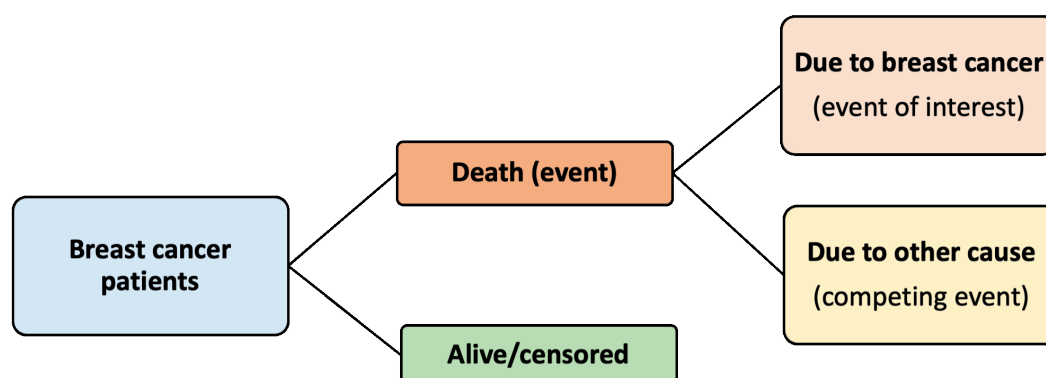


Figure 1. Schematic presentation of competing risks model for breast cancer patients.

Statistical analysis

Internal consistency was assessed in the data. Descriptive statistics such as mean $\pm$ SD and median (interquartile range) are presented for normally distributed data and skewed distribution, respectively. For categorical variables, the proportion is used. Accounting for competing risk factors, two different families of regression models are applied. The Cox model described the effect of covariates on the outcome's cause-specific hazard (CSH),⁹ while the Fine and Gray model¹⁰ dealt with the subdistribution hazard function. Both models consider competing risks, but their interpretations differ (Figure 2). A cause-specific hazard (CSH) model's regression coefficient represented

the relative effect of a certain covariate on the relative change in the rate of occurrence of the event of interest in subjects who were event-free at the time. The impact of covariates on the cumulative incidence function for the event of interest could be estimated using the subdistribution hazard ratio (SHR) model. The details of the mathematical models can be found in Prentice *et al.*⁹ and Fine and Gray.¹⁰ The CSH and SDH models' estimation results are reported as hazard ratios (HR) with a 95% confidence interval (95% CI). Statistical software STATA version 15.1, Stata Corp, Texas, USA, was used for all statistical analysis. The $p < 0.05$ was considered statistically significant.

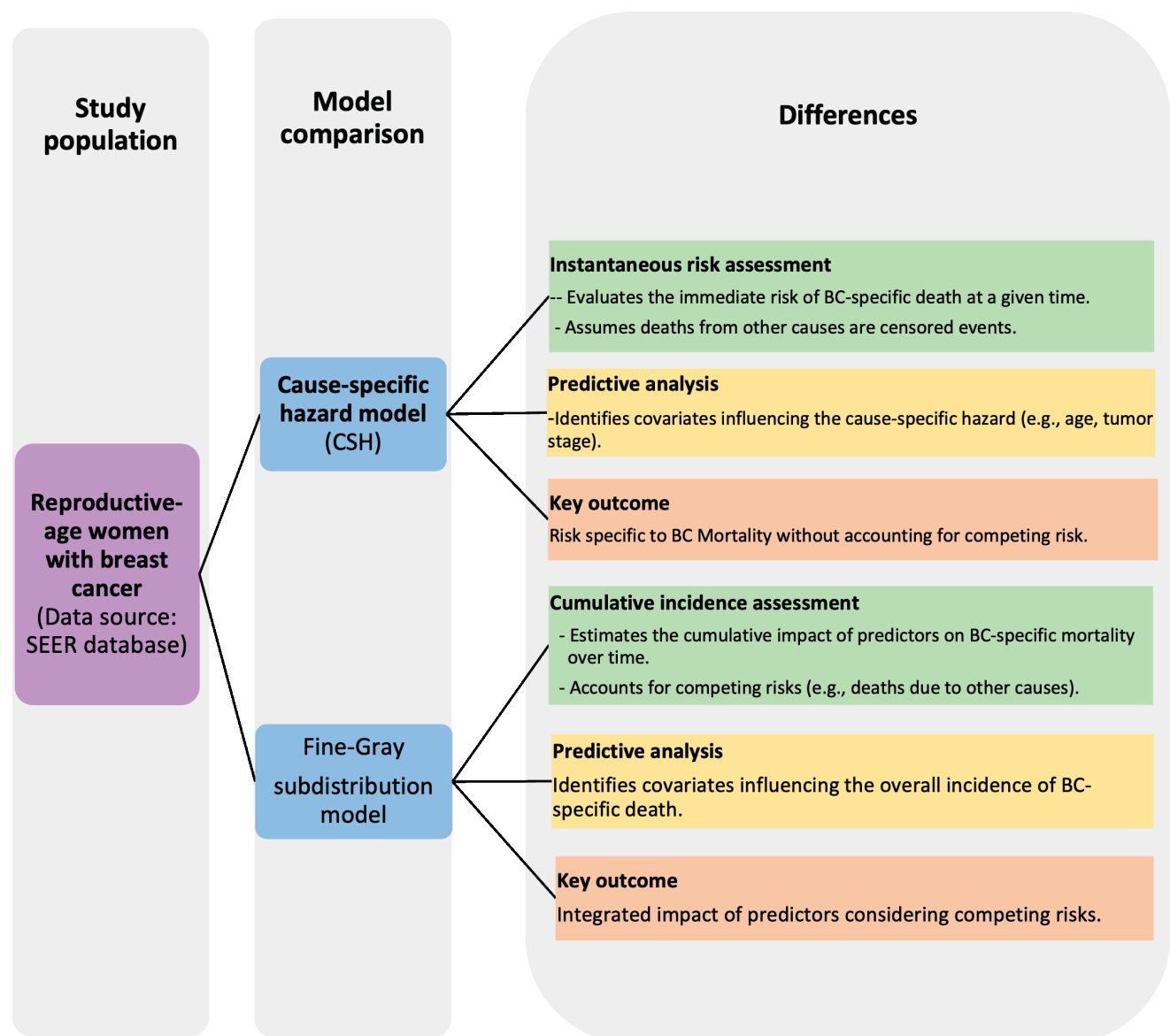


Figure 2. Distinctions between cause-specific hazard and Fine-Gray models in competing risk analysis.

Results

Patient characteristics

A total of 67,063 female BC patients within the reproductive age range were included in the analysis. The majority of patients were diagnosed with stage II breast cancer (42.5%), followed by stage I (37.2%), stage III (15.6%), and stage IV (4.7%). Hormone receptor

status was positive in 79.6% of patients, while 20.4% had negative hormone receptor status. During the follow-up period, there were 7,707 deaths, with 6,813 attributed to BC and 894 to other causes. The mean age of BC patients was 42.7 ± 5.4 years. The overall survival period ranged from 1 to 107 months, with an average survival time of 64. Detailed patient characteristics are summarized in Table 1.

Table 1. Distribution of outcomes concerning demographic and tumor characteristics.

Variables	Categories	Frequency (%)
Year of diagnosis	2010	10,630 (15.85)
	2011	11,210 (16.72)
	2012	11,170 (16.66)
	2013	11,363 (16.94)
	2014	11,257 (16.79)
	2015	11,433 (17.05)
Age (years) [Mean $\pm$ SD]		42.7 $\pm$ 5.4
Age group (years)	40-49	51,357 (76.58)
	30-39	13,938 (20.78)
	15-29	1,768 (2.64)
Race and origin	Hispanic (all races)	11,464 (17.09)
	Non-Hispanic American Indian/Alaska Native	38,208 (56.97)
	Non-Hispanic Asian or Pacific Islander	8,808 (13.13)
	Non-Hispanic Black	433 (0.65)
	Non-Hispanic White	7,871 (11.74)
	Non-Hispanic Unknown Race	279 (0.42)
SEER stage	Local	37,285 (55.6)
	Regional	26,170 (39.02)
	Distant	3,608 (5.38)
AJCC stage	Stage I	24,970 (37.23)
	Stage II	28,478 (42.46)
	Stage III	10,433 (15.56)
	Stage IV	3,182 (4.74)
Breast subtype	HR+/HER2+ (Luminal B)	9,710 (14.48)
	HR+/HER2- (Luminal A)	43,694 (65.15)
	HR-/HER2+ (HER2 enriched)	3,834 (5.72)
	HR-/HER2- (Triple negative)	9,825 (14.65)
ER status	Positive	52,401 (78.14)
	Negative	14,662 (21.86)
PR status	Positive	47,689 (71.11)
	Negative	19,374 (28.89)
Derived HER2	Positive	13,544 (20.2)
	Negative	53,519 (79.8)
Survival months [Mean $\pm$ SD]		64 $\pm$ 24.9
Patient status	Alive	59,356 (88.5)
	BC mortality	6,813 (10.2)
	Other-cause mortality	894 (1.3)

Cumulative incidence of cause-specific mortality

The cumulative incidence of BC mortality at 5 years was 4.8%, and at 9 years was 8.1%. In comparison, the cumulative incidence of other-cause mortality at 5 and 9

years was 0.95%, and 1.7%, respectively. Figure 3 illustrates the cumulative incidence functions (CIF) for both BC and other-cause mortality.

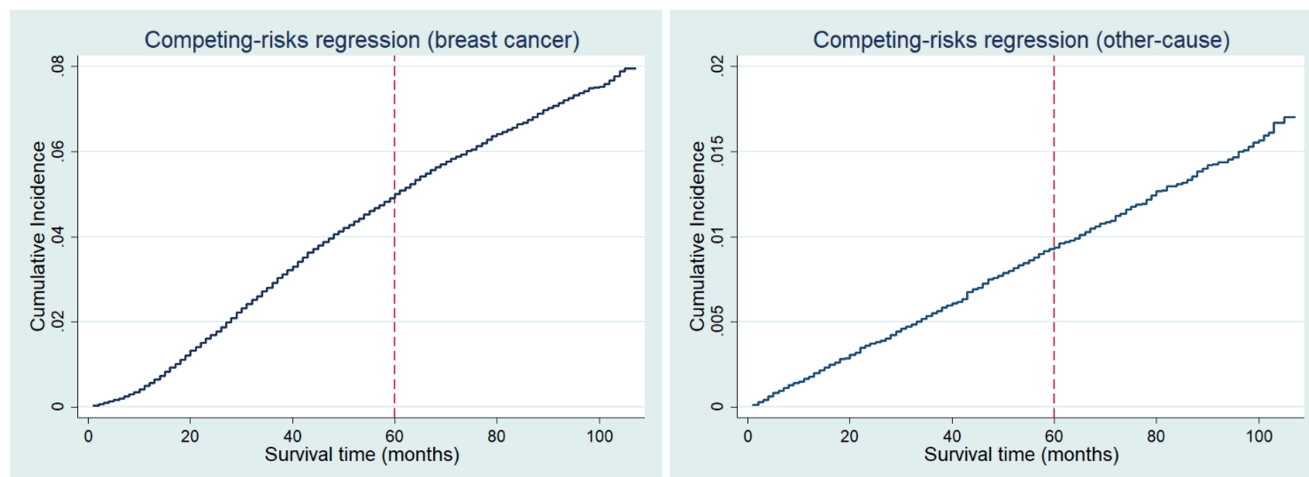


Figure 3. Overall CIF comparison between breast cancer (left) and non-breast cancer (right).

Predictors of breast cancer-specific mortality

In the univariate analysis, several factors were significantly associated with BC mortality, including age at

diagnosis, race, tumor stage, and hormone receptor status (Figure 4 and Figure 5).

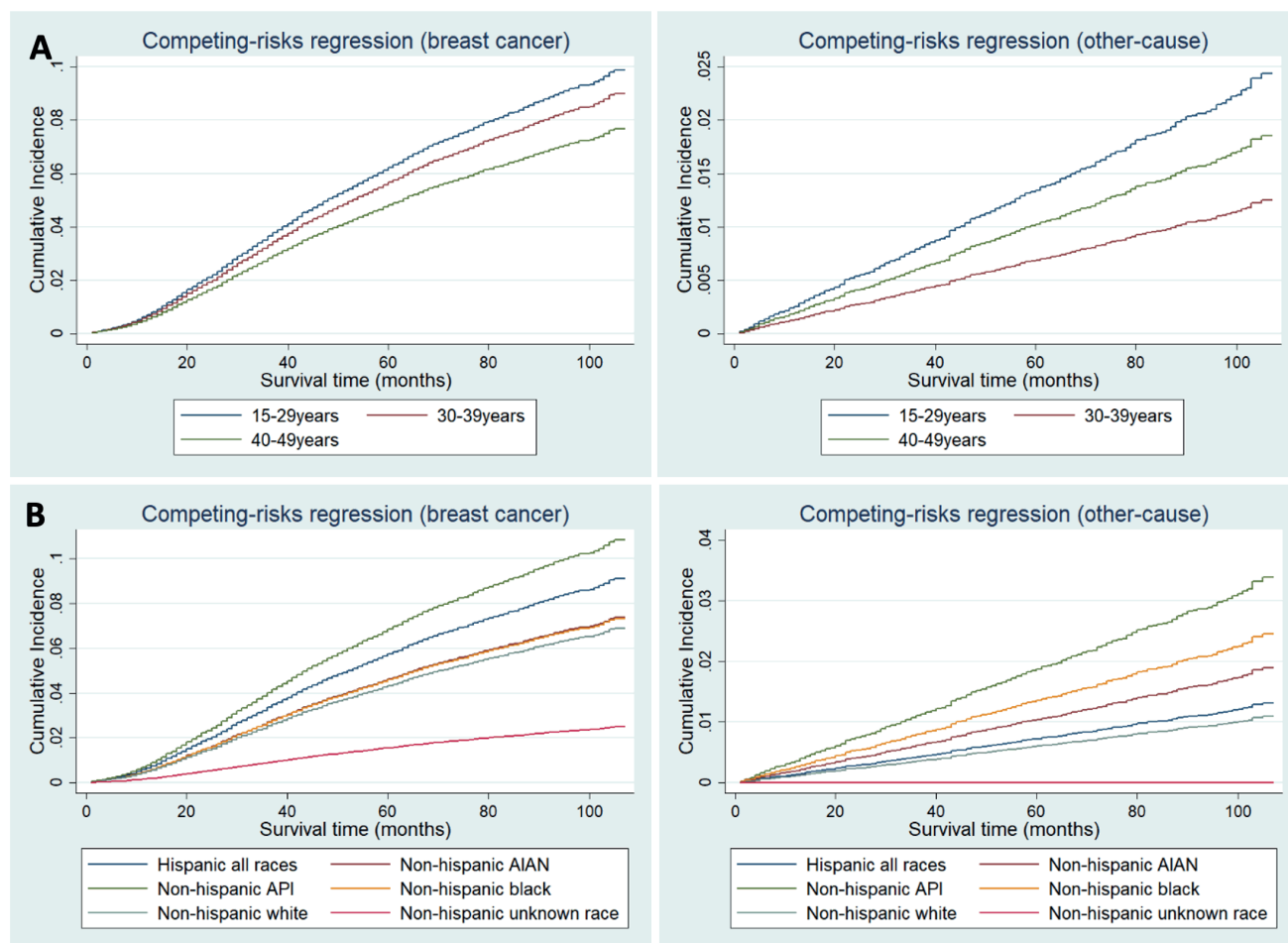


Figure 4. CIF comparison of demographic variables between breast cancer mortality (left) vs other-cause mortality (right). A: age group, B: race and origin.

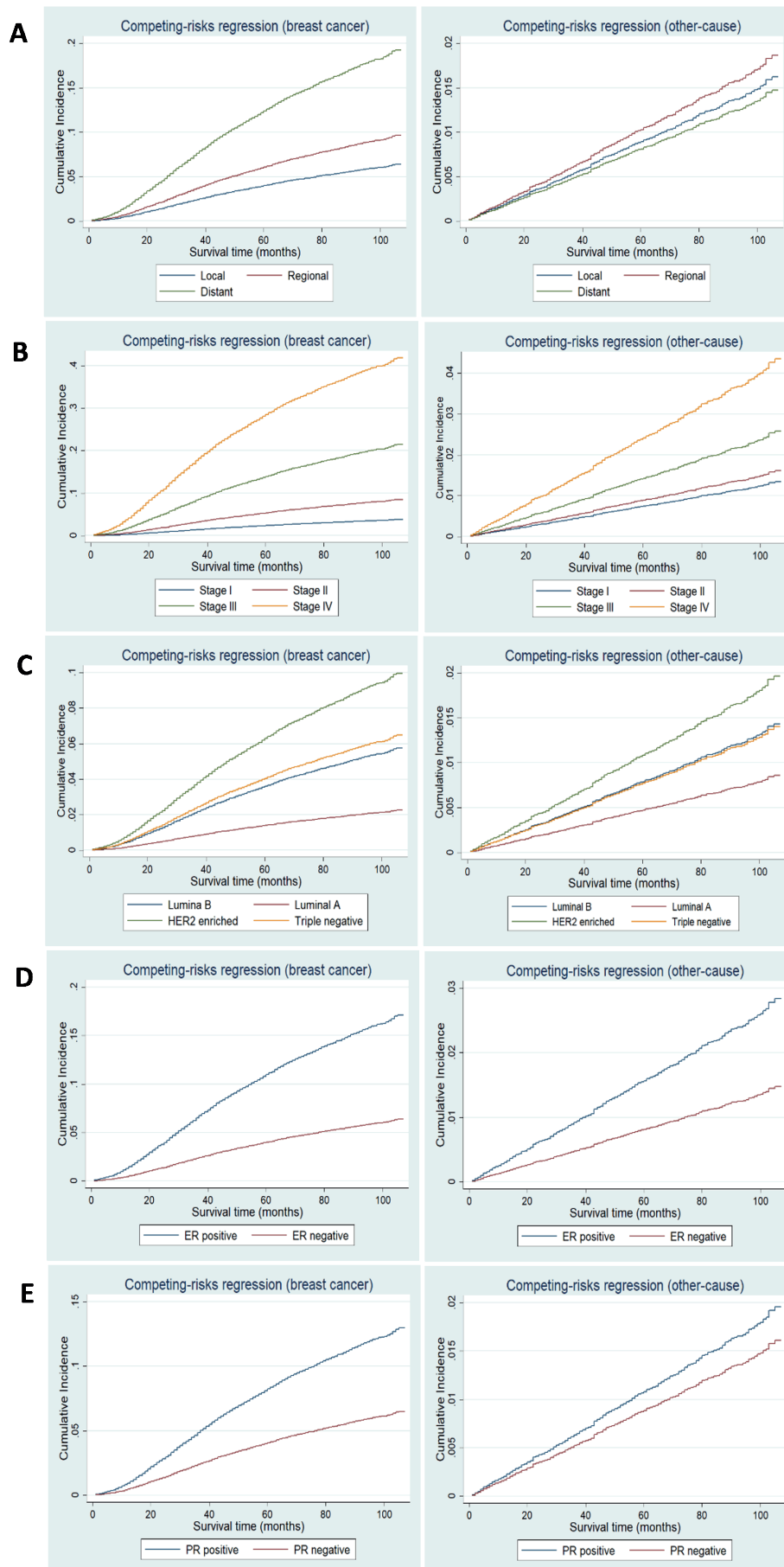


Figure 5. CIF comparison of tumor characteristics between breast cancer mortality (left) vs other-cause mortality (right).
A: SEER staging, B: AJCC staging, C: breast subtypes, D: ER status, E: PR status.

Multivariate competing risk analysis

The CSH and SDH models were used to calculate the cumulative incidence of death due to BC and other causes. Because of collinearity, HER2 status, and breast subtype parameters were omitted from the multivariate analysis.

Table 2 shows the hazard ratios for BC and other-cause mortality for each analyzed factor. The findings reveal that while CSH and SDH models give comparable results regarding HR estimates, they differ regarding cause-specific events.

Table 2. Multivariate results under the cause-specific Cox model and subdistribution competing risk model.

Parameters	Cause-specific hazard model CSH (95% CI)		Subdistribution hazard ratio model SHR (95% CI)	
	Breast cancer mortality	Other-cause mortality	Breast cancer mortality	other-cause mortality
Age group (years) (40-49 as Ref.)				
30-39	1.28 (1.20, 1.37)	0.62 (0.50, 0.76)	1.29 (1.20, 1.38)	0.61 (0.49, 0.75)
15-29	1.4 (1.21, 1.63)	1.07 (0.70, 1.64)	1.42 (1.20, 1.64)	1.05 (0.69, 1.61)
Race and origin (Hispanic all races as Ref.)				
Non-Hispanic American Indian/Alaska Native	0.86 (0.80, 0.94)	1.33 (1.05, 1.69)	0.86 (0.79, 0.93)	1.35 (1.06, 1.71)
Non-Hispanic Asian or Pacific Islander	1.3 (1.19, 1.43)	2.6 (2.00, 3.39)	1.28 (1.16, 1.41)	2.54 (1.95, 3.31)
Non-Hispanic Black	0.82 (0.57, 1.18)	1.75 (0.76, 4.00)	0.82 (0.57, 1.19)	1.77 (0.77, 4.03)
Non-Hispanic White	0.74 (0.66, 0.84)	0.61 (0.41, 0.91)	0.76 (0.66, 0.84)	0.62 (0.41, 0.93)
Non-Hispanic Unknown Race	0.2 (0.07, 0.63)	-	0.2 (0.07, 0.62)	-
SEER stage (local as Ref.)				
Regional	1.61 (1.46, 1.77)	1.23 (0.97, 1.55)	1.6 (1.45, 1.77)	1.21 (0.95, 1.52)
Distant	2.73 (2.15, 3.46)	0.27 (0.04, 1.98)	2.77 (2.12, 3.61)	0.23 (0.03, 1.64)
AJCC stage (Stage I as Ref.)				
Stage II	2.3 (2.03, 2.61)	1.18 (0.94, 1.48)	2.3 (2.03, 2.62)	1.19 (0.95, 1.49)
Stage III	4.88 (4.20, 5.67)	1.65 (1.19, 2.30)	4.86 (4.17, 5.66)	1.59 (1.15, 2.20)
Stage IV	11.82 (9.00, 15.54)	14.29 (1.89, 38.29)	11.3 (8.37, 15.25)	11.22 (1.48, 45.32)
Positive regional nodes	1.05 (1.01, 1.09)	1 (0.93, 1.09)	1.05 (1.01, 1.09)	0.98 (0.96, 1.03)
ER negative	3.24 (2.67, 3.92)	2.04 (1.24, 3.37)	3.23 (2.65, 3.95)	1.81 (1.10, 2.99)
PR negative	2.5 (2.27, 2.75)	1.31 (1.00, 1.72)	2.47 (2.23, 2.73)	1.21 (0.92, 1.59)

Note: CSH: cause-specific hazard ratio, SHR: subdistribution hazard ratio, CI: confidence interval, ER: estrogen receptor, PR: progesterone receptor. Ref.: reference category.

Breast cancer mortality

Both models show that age group, race & origin, SEER stage, AJCC stage, positive regional node, ER status, PR status, and breast subtypes are statistically significant ($p < 0.05$) for patients who have died due to BC. Patients under 40 years had a significantly higher risk of BC mortality compared to those aged 40-49 years. Non-Hispanic Asian or Pacific Islander patients have a higher risk of BC mortality than Hispanic patients. In contrast, non-Hispanic American Indian/Alaska Native and non-Hispanic White patients have significantly smaller risk of death. Patients with regional and distant-stage disease had 1.6 times and 2.7 times increased risk of BC mortality, respectively, as compared to patients with local stages. Furthermore, patients with stages II, III, and IV have an escalated risk of BC mortality (HR=2.30, HR=4.86, and HR=11.30, respectively) compared to those with stage I. In

addition, patients with ER and PR negative are associated with a greater risk of BC mortality than the patients with ER and PR positive, respectively.

Other cause mortality

Patients aged 30-39 years are found to have significantly less risk of other-cause mortality (HR=0.61) than those aged 40-49 years. Non-Hispanic American Indian/Alaska Native (HR=1.35) and Asian or Pacific islander (HR=2.54) patients have a greater risk of other-cause mortality than Hispanic-origin patients. However, non-Hispanic white race patients have a more negligible risk of other-cause mortality (HR=0.62). Stage III and IV patients also have a significantly higher risk of other-cause mortality. Patients with ER-negative were associated with a substantially greater risk of other-cause mortality than the ER-positive patients (HR=1.81).

Discussion

In this study, we focused on BC mortality among reproductive-age women, considering other-cause mortality as competing events. Recognizing that these competing events can alter the probability of the primary event, we utilized competing risk techniques such as the cumulative incidence function, cause-specific hazard, and subdistribution hazard models for our analysis.

Despite competing risks, our results have significant implications for refining and adjusting absolute risk estimates for BC patients in reproductive age groups. We found that the 9-year cumulative incidence of BC mortality was 8.1%, while other-cause mortality was 1.7%. This study is among the first to provide estimations of BC- and other-cause-specific cumulative incidences of death using competing risks analysis for reproductive-age women.

We identified several established prognostic markers influencing survival or death due to BC in the presence of competing events, including age at diagnosis, race, and origin, staging, ER status, and PR status. These predictors align with published global literature, reinforcing the high risk of BC mortality within the first few years post-diagnosis.¹²⁻¹⁴

Our analysis revealed that younger age groups have an increased risk of BC mortality compared to older age groups, consistent with the conclusions of Keegan *et al.*, who noted higher BC mortality in adolescents and young adults than in patients aged 40-64 years.¹⁵ Interestingly, race plays a critical role; for instance, non-Hispanic American Indian/Alaska Natives exhibited a lower risk of BC mortality but higher hazards for other-cause mortality.¹² Similarly, non-Hispanic Asians or Pacific Islanders faced a greater risk of other-cause mortality.¹³ These observations necessitate further race-specific subgroup analyses to understand the reasons behind these differences.

A notable finding is the higher hazard of BC mortality due to distant-stage cancer compared to a lower risk for other-cause mortality. This is consistent with previous studies, which have shown that the long-term risk of distant metastasis remains substantial in women with non-metastatic breast cancer, affecting survival rates adversely once metastasis is detected.¹⁶ Furthermore, young age at diagnosis (<40 years) significantly impacts prognosis, with worse outcomes observed in particular breast cancer subtypes.¹⁷ These insights emphasize the critical need for continuous monitoring and tailored treatment strategies for patients diagnosed at a distant stage.

Conversely, competing risks of death from other causes remain significant but lower in magnitude. Historical data indicates shifts in the causes of death over time, suggesting improvements in breast cancer treatment and management but highlighting the importance of addressing other health risks that may affect this population.¹⁸

The findings from this study have important clinical implications. The high mortality risk associated with younger age and advanced stage at diagnosis underscores the need for targeted screening and early detection efforts in reproductive-aged women. Healthcare providers should

be vigilant in identifying and managing breast cancer in younger women, considering their unique risk profile and the potential for more aggressive disease. Given the poor prognosis associated with hormone receptor-negative status, there is a critical need for research into novel therapeutic approaches and personalized treatment plans to improve outcomes for this subgroup.

Limitations

While this study provides valuable insights into cause-specific mortality among reproductive-age women with breast cancer, certain limitations should be acknowledged.

First, the retrospective nature of the analysis inherently limits the ability to establish causality. Although we utilized a robust database (SEER) with high-quality data collection standards, the study design is observational and subject to potential biases.

Second, excluding patients with incomplete information on key variables (e.g., tumor stage, hormone receptor status) may have introduced selection bias. While this approach is necessary for ensuring data integrity, it could lead to the underrepresentation of certain subgroups, potentially affecting the generalizability of the findings. Future studies should consider employing imputation or sensitivity analyses to account for missing data.

Lastly, the SEER database lacks detailed information on certain risk factors, such as reproductive history, genetic predispositions, or lifestyle factors, which may influence both breast cancer and competing mortality risks. Including these variables in future research could provide a more comprehensive understanding of mortality predictors.

Despite these limitations, our study demonstrates the utility of competing risk models in understanding mortality patterns in this specific demographic, providing a foundation for further investigation and targeted interventions.

Conclusion

In summary, this study evaluated mortality among reproductive-age women, focusing on deaths attributable to BC in the presence of competing causes of death. Key factors influencing BC mortality include age (with younger women <40 years at higher risk), race and origin, staging, ER-negative status, and PR-negative status. Using a competing risk model provides a more accurate estimate of mortality risks, offering valuable insights for clinical practice. Targeted screening, early detection, and the development of effective treatment strategies are essential for improving survival outcomes in this vulnerable population. Future research should aim to address the limitations of this study and further our understanding of breast cancer prognosis in reproductive-aged women.

Ethical considerations

The SEER database is publicly available and does not contain identifiable patient information. Thus, ethical approval and informed consent were not required for this study.

Data availability statement

All data are available publicly through SEER.

Conflict of interest

There is no conflict of interest.

Acknowledgements

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