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Nomogram to predict contralateral breast cancer risk in breast cancer survivors

A SEER-based study

Jiaci Tong, MD, Dewei Tan, MD, Jing Ma, MD, Ye Hu, MD, Man Li, PhD*

Abstract

The main purpose of this study was to build a prediction model for patients with contralateral breast cancer (CBC) using competing risks methodology. The aim is to help clinicians predict the probability of CBC in breast cancer (BC) survivors.

We reviewed data from the Surveillance, Epidemiology, and End Results database of 434,065 patients with BC. Eligible patients were used to quantify the association between the development of CBC and multiple characteristics of BC patients using competing risk models. A nomogram was also created to facilitate clinical visualization and analysis. Finally, the stability of the model was verified using concordance index and calibration plots, and decision curve analysis was used to evaluate the clinical utility of the model by calculating the net benefit.

Four hundred thirty-four thousand sixty-five patients were identified, of whom 6944 (1.6%) developed CBC in the 10 years follow-up. The 10-year cumulative risk of developing CBC was 2.69%. According to a multivariate competing risk model, older patients with invasive lobular carcinoma who had undergone unilateral BC surgery, and whose tumor was better differentiated, of smaller size and ER-negative/PR-positive, had a higher risk of CBC. The calibration plots illustrated an acceptable correlation between the prediction by nomogram and actual observation, as the calibration curve was closed to the 45° diagonal line. The concordance index for the nomogram was 0.65, which indicated it was well calibrated for individual risk of CBC. Decision curve analysis produced a wide range of risk thresholds under which the model we built would yield a net benefit.

BC survivors remain at high risk of developing CBC. Patients with CBC have a worse clinical prognosis compared to those with unilateral BC. We built a predictive model for the risk of developing CBC based on a large data cohort to help clinicians identify patients at high risk, which can then help them plan individualized surveillance and treatment.

Abbreviations: AAPC = average annual percentage change, APC = annual percentage change, BC = breast cancer, BCM = breast-conserving mastectomy, CBC = contralateral breast cancer, C-index = concordance index, CPM = contralateral prophylactic mastectomy, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, PBC = primary breast cancer, SEER = Surveillance, Epidemiology, and End Results Program, ULM = unilateral mastectomy.

Keywords: contralateral breast cancer, epidemiology and end results database, fine and gray model, nomogram, prognosis, surveillance

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The datasets generated and/or analyzed during the current study are available in the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/).

Because the SEER database is a publicly available anonymous database, this study was exempt from Institutional Review Board approval. The author Tong has gotten access to the SEER database (accession number: 17366-Nov2018).

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The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Breast cancer (BC) is one of the most frequently diagnosed cancers. It ranks as the second cause of cancer mortality in women worldwide.[1] In the past half century, with improved surveillance and increased treatment options, BC survivors have a longer life expectancy. However, as a result, an increasing number of patients with BC are at risk of developing secondary tumors.[2,3] Following a primary breast cancer (PBC), contralateral breast cancer (CBC) is the most common subsequent cancer, accounting for 30% to 50% of all subsequent cancers.[2–4] Surviving BC patients are 2 to 3 times more likely to develop CBC compared to healthy women.[5,6]

Increasing numbers of BC patients are opting for prophylactic contralateral mastectomy (PCM).[7,8] In practice, however, the probability of CBC in patients without genetic mutations is extremely low. Furthermore, extensive studies have demonstrated that prophylactic bilateral surgery not only fails to prolong the survival of BC patients, but also causes more complications than unilateral mastectomy (ULM).[9–11] There is, therefore, an urgent need for individualized predictive models of CBC risk to enable surgeons and women themselves to decide on prevention and treatment strategies, and to avoid over-screening and treatment when CBC risk is low.

In previous CBC studies, there has often been bias because of small cohorts of patients and limited follow-up time. Most studies have been performed using Cox proportional hazards regression models and have not considered competing risks for other cancer outcomes, especially for the occurrence of small probability events. For example, a patient who dies of a non-neoplastic disease is unlikely to die of cancer. Thus, the 2 are competing events and mutually exclusive. When competing events exist, traditional survival analysis methods treat competing events as right-censored when conditional only on the incidence of the event of interest, resulting in an overestimation of the true observed outcome.[12,13]

In this study, we screened 434,065 BC cases based on the number of enrollments, the number of primary cancers, and the primary site of the cancer. We established a risk competition model based on this large data cohort. A competing risk model was also developed, and the risk factors associated with CBC were demonstrated by plotting nomograms. The model was validated by concordance index (C-index), calibration curves and decision analysis, which yielded good validation results.

2. Methods

2.1. Data sources

The Surveillance, Epidemiology, and End Results (SEER) database, managed by the National Cancer Institute, compiles and publishes cancer population, incidence, and survival data from population-based cancer registries in 18 states and covers approximately 28% of the US population.[14] In this study, we selected female CBC patients from the SEER database via SEER*Stat software (version 8.3.6) to evaluate potential risk factors for CBC.

2.2. Inclusion and exclusion criteria

Due to the lack of specific codes to identify CBC patients in SEER, we further established screening rules by analyzing the number of enrollments, time of enrollment, number of primary cancers and the specific site of each primary cancer in the included patients. All included cases were coded according to the International Classification of Diseases of Oncology, third revision, with primary site code C50.9 and histological codes 8000/3-9020/3. Patients with PBC enrolled between January 2005 and January 2015 were included in our cohort if they satisfied the following criteria: the breast was the first and only cancer site; complete survival information and clinical characteristics data were available, and there was a follow-up time of more than 0 months. Tumor node metastasis staging was determined by the 6th American Joint Committee on Cancer Staging Manual delineation. We subsequently excluded cases with only death certificate records or autopsies. In our study, patients who were lost to follow-up before the occurrence of a competing event or event of interest, or who had neither an outcome event nor a competing event by the end of follow-up, were recorded as truncated data. 434,065 patients met all our selection criteria and were included in the cohort. The selection criteria are detailed in the flowchart (Fig. 1).

2.3. Joinpoint regression analysis

We filtered patients with CBC over a 40-year period from 1976 to 2015 and stratified them by age group. The age-specific incidence rates were calculated for different age groups, and the annual percentage change (APC) and average APC were calculated by fitting Joinpoint models to the CBC incidence rates of the 2 cohorts separately. The general trend of CBC over the last 40 years and the risk of CBC for different age groups were further evaluated. The model was fitted to analyze the turning point of CBC incidence change between years, with APC >0 indicating an increasing incidence annually and APC >0 indicating a decreasing incidence annually. If there was no turning point, then APC = average APC, indicating an overall monotonic increasing or decreasing trend for the dataset.[15]

2.4. Assessment of variables

We extracted various determinants associated with CBC risk, including age at initial diagnosis (classified as $\leq$50 and $>$50 years), tumor size in centimeters ($\leq$1 cm, 1–3 cm, 3–5 cm, $>$5 cm), number of positive lymph nodes, grade (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated), ER and PR status (positive and negative), histological type (invasive ductal carcinoma [IDC], invasive lobular carcinoma [ILC], invasive ductal, and lobular carcinoma and other types), first surgical treatment with PBC (no surgery, breast-conserving mastectomy [BCM], ULM and contralateral prophylactic mastectomy [CPM]), and tumor node metastasis stage, adjusted according to the 6th American Joint Committee on Cancer. The primary endpoint was the diagnosis of CBC, and any other cause of death was considered a competing event.

2.5. Competitive risk modeling

Instead of traditional survival analysis, the proportional subdistribution hazards regression model is more appropriate for estimating unbiased risk of CBC in the presence of competing events (in our analysis, the death from any causes). In the presence of competing risks, the Kaplan–Meier method is biased to estimate the cumulative incidence of competing events as truncated data. This is because the Kaplan–Meier method treats competing events as censored when estimating the incidence of an outcome event, so is often overestimated or even contradictory to the fact. This is why the competing risks model should be used.[16] It is an analytical method for dealing with multiple potential outcome survival data (including competing risk events). It includes the time horizon of failure and the endpoint events leading to failure, which may be multiple, and these potential endpoint events are called "competing risk" events.[17]

2.6. Nomogram establishment and validation

To provide clinicians with a quantitative tool for predicting the individual probability of developing CBC, we built nomogram plots based on competing risk models. The sum of independent factors is located on the total point axis and corresponds down the response axis to determine the probability of CBC occurring at 1, 5, and 10 years. We evaluated the validity of the column line graphs using 100 bootstrap resamples for calibration curves and C-index to measure classification accuracy. The C-index for the nomogram was 0.65, which ranges from 0.5 to 1.0, with a higher C-index indicating better model discrimination.[18] The calibration curve was generated to validate the calibration by comparing the estimated risk with the actual risk. When the predicted values fall on the diagonal line, this indicates that the model is perfectly

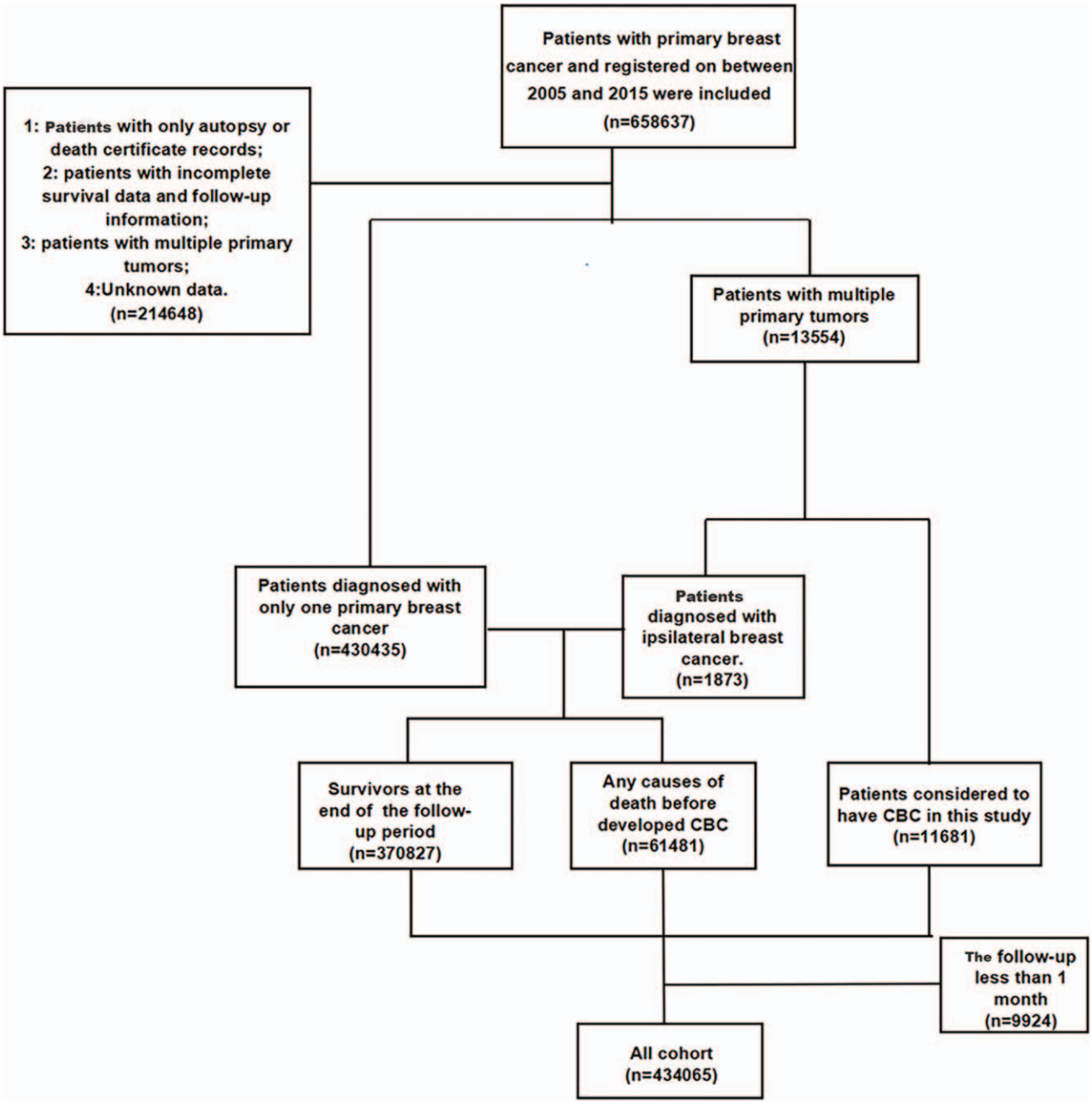

Figure 1. Flow diagram of the selection process for the study. CBC = contralateral breast cancer, n = number.

calibrated. However, there is no direct clinical interpretation of the C-index as well as the calibration curve. Therefore, we also applied decision curve analysis – a new method that evaluates predictive models in terms of clinical consequences by calculating net benefits. A model is clinically useful if its application yields a greater net benefit.[19]

2.7. Statistical analysis

All the statistical analyses were carried out using the R version 3.6.3 software (Institute of Statistics and Mathematics, Vienna, Austria. www.r-project.org). Joinpoint regression analysis used Joinpoint software (version 4.3.1.0). Statistical significance was determined as $P < .05$ for both sides.

3. Results

3.1. Trends in CBC incidence over 40 years and changes in incidence trends by age group

We first examined trends in the development of CBC from 1976 to 2015 and found that the total annual incidence of CBC in BC survivors steadily increased (Fig. 2A), but the incidence rate increased differently in different age groups. Of the 36,466 CBC

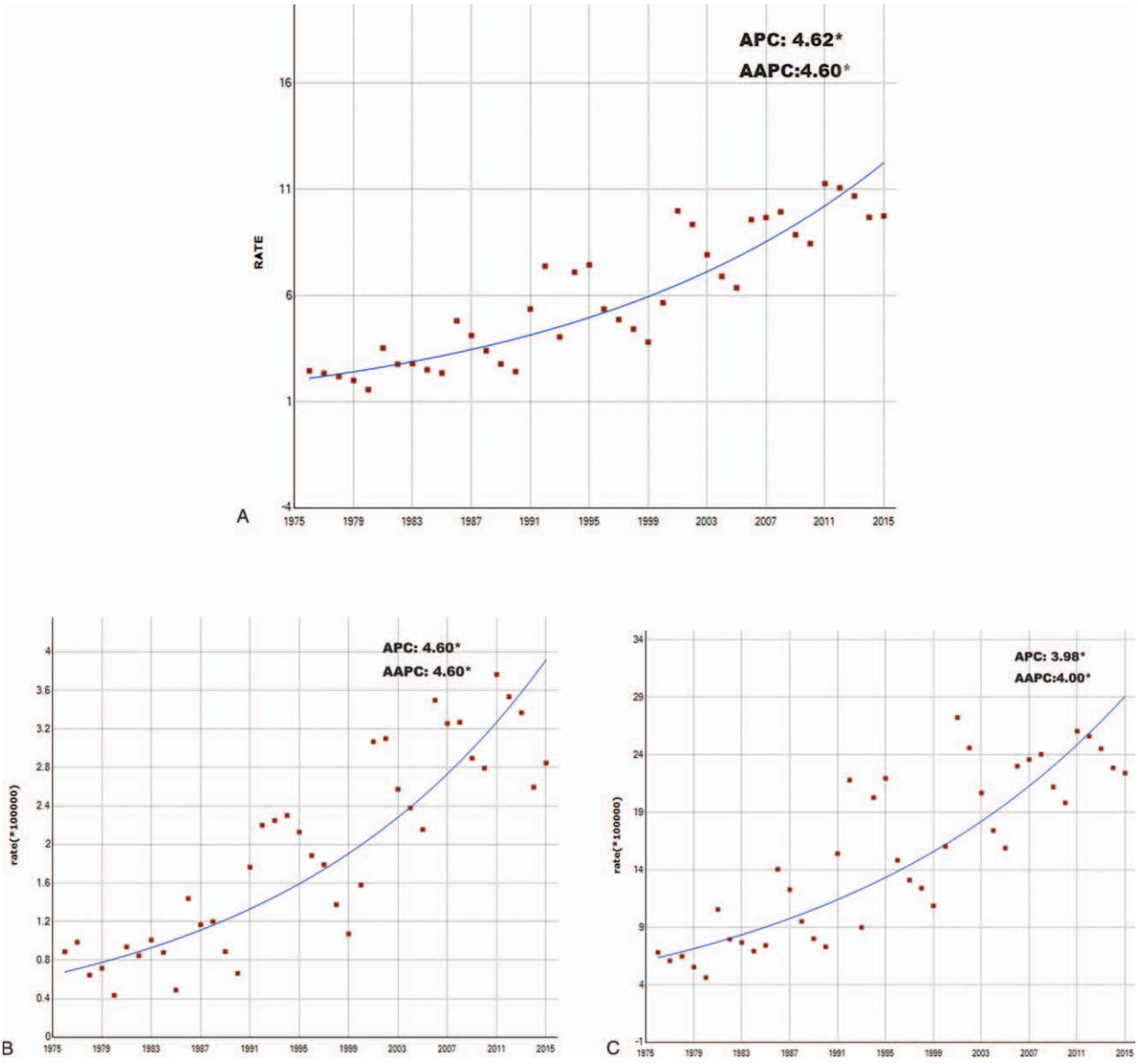

Figure 2. Trends in BBC incidence rates between 1976 and 2015 (A). Rate of BBC from 1976 to 2015 by age at diagnosis: ≤50 years old (B), >50 years old (C). AAPC = average annual percentage change, APC = annual percentage change. *: $P < .05$ per 100,000 persons and age-adjusted to the 2000 US standard population.

cases screened between 1976 and 2015, 7252 (19.9%) were younger than 50 at diagnosis and 29,214 (80%) were older. The APC was 4.60% in the younger group (Fig. 2B) and 3.98% in the older group (Fig. 2C). This indicates that the younger cohort faced a higher risk of CBC occurrence compared to the older group.

3.2. Cumulative incidence of CBC from 2005 to 2015

From 2005 to 2015, we screened a total of 434,065 female BC patients. Of these, 6944 (1.60%) patients developed CBC and 60,762 (14.0%) patients died from any causes at the end of the follow-up period (Table 1). The 10-year cumulative incidence was lower and statistically significant in the younger age group, poorer differentiation, earlier stage, smaller tumor size, CPM by surgery, PR-positive, and IDC. The different degree of differentiation had a different risk of CBC, probably due to the higher mortality rate, which prevented the development of CBC. The cumulative incidence function curves among subgroups are plotted in Figure 3.

3.3. Risk predictors for CBC after a confirmed BC diagnosis

Multivariate analysis showed that age, differentiation, histological type, tumor size, type of surgery, and ER/PR status were strong predictors of CBC, with no significant differences in the number and stage of invasive lymph nodes for the development of

Table 1

Crude incidence and 10-year cumulative incidence of CBC among female patients with initial breast cancer.

Characteristics cumulative incidence	Overall patients (n)	CBC patients (n)	Crude incidence (%)	10 years CBC(%) Incidence (%) (95% CI)	*P* value
Total	434,065	6944	1.60	2.69 (2.61, 2.78)	
Age (yr)					<.001
≤50	112,724	5292	4.69	2.48 (2.32, 2.63)	
>50	321,341	1652	0.51	2.76 (2.68, 2.87)	
Grade					<.001
Well	97,737	1759	1.8	2.93 (2.75, 3.11)	
Moderate	188,469	3146	1.67	2.73 (2.61, 2.86)	
Poor	145,428	2004	1.38	2.48 (2.34, 2.62)	
Un	2431	35	1.44	2.22 (1.35, 3.08)	
stage					<.001
0	221	3	1.36	1.89 (0.28, 4.88)	
I	211,910	3462	1.63	2.82 (2.70, 2.95)	
II	157,852	2465	1.56	2.65 (2.51, 2.78)	
III	50,647	878	1.73	2.67 (2.44, 2.89)	
IV	13,435	136	1.01	1.31 (1.05, 1.58)	
Lymph node					.018
0	291,930	4746	1.63	2.82 (2.72, 2.93)	
1	100,246	1503	1.5	2.46 (2.31, 2.62)	
2	24,846	404	1.63	2.42 (2.14, 2.71)	
3	17,043	291	1.71	2.34 (2.01, 2.67)	
Tumor size					<.001
1	108,220	1767	1.63	2.82 (2.65, 2.99)	
2	240,718	3767	1.56	2.66 (2.55, 2.77)	
3	53,326	831	1.56	2.49 (2.27, 2.71)	
4	31,801	579	1.82	2.89 (2.57, 3.22)	
Surgery					<.001
ULM	120,172	2872	2.39	3.5 (3.34, 3.67)	
CPM	44,360	436	0.98	1.15 (0.99, 1.31)	
BCM	250,554	3456	1.38	2.56 (2.45, 2.67)	
No	18,979	180	0.95	1.29 (1.07, 1.51)	
ER					.035
Negative	79,878	1270	1.59	2.87 (2.68, 3.07)	
Positive	354,187	5674	1.6	2.63 (2.54, 2.72)	
PR					<.001
Negative	125,320	1848	1.47	2.59 (2.44, 2.74)	
Positive	308,745	5096	1.65	2.72 (2.62, 2.82)	
Histology					<.001
IDC	343,808	5137	1.49	2.61 (2.51, 2.70)	
ILC	36,308	786	2.16	3.14 (2.86, 3.42)	
IDC + ILC	27,215	614	2.26	3.46 (3.12, 3.80)	
Other	26,734	407	1.52	2.37 (2.10, 2.65)	

BCM = breast-conserving mastectomy, CBC = contralateral breast cancer, CI = confidence interval, CPM = contralateral prophylactic mastectomy, IDC = infiltrating duct carcinoma, ILC = infiltrating lobular carcinoma, moderate = moderately differentiated, poor = poor differentiated, tumor size: 1 = ≤1 cm, 2 = 1 to 3 cm, 3 = 3 to 5 cm, 4 = >5 cm.
ULM = unilateral mastectomy, un = undifferentiated, well = well differentiated.

CBC ($P > .01$). Older age, better grade, smaller tumor size, ILC, ER-negative/PR-positive, and ULM were factors strongly associated with the development of CBC. Meanwhile, the stage and the number of infiltrating lymph nodes were not statistically significant for CBC. Among the factors, surgical approach, degree of differentiation, histological type, and ER status were the 3 most important predictors of CBC risk (Table 2).

3.4. Visual model development and validation

A simplified model was determined based on the Bayesian information criterion. The final model was selected considering both statistical significance and Bayesian information criteria. The nomogram shown in Figure 4 was constructed based on the final model. In using this nomogram, the patient's variable values were first located on each axis, then lines were drawn upward to identify the points for each variable. The sum of these points was then located on the total points axis, and finally the 3-year, 5-year, and 10-year risk probabilities for CBC were predicted based on the sum.

Figure 5 shows the calibration curve plots for the 5-year and 10-year cumulative incidence rates. The C-index for the nomogram was 0.65, which indicated it was well calibrated for the individual risk of CBC. The calibration curves close to the 45° line show acceptable agreement between the predicted and actual probabilities of CBC occurrence (Fig. 5A and 5B). In

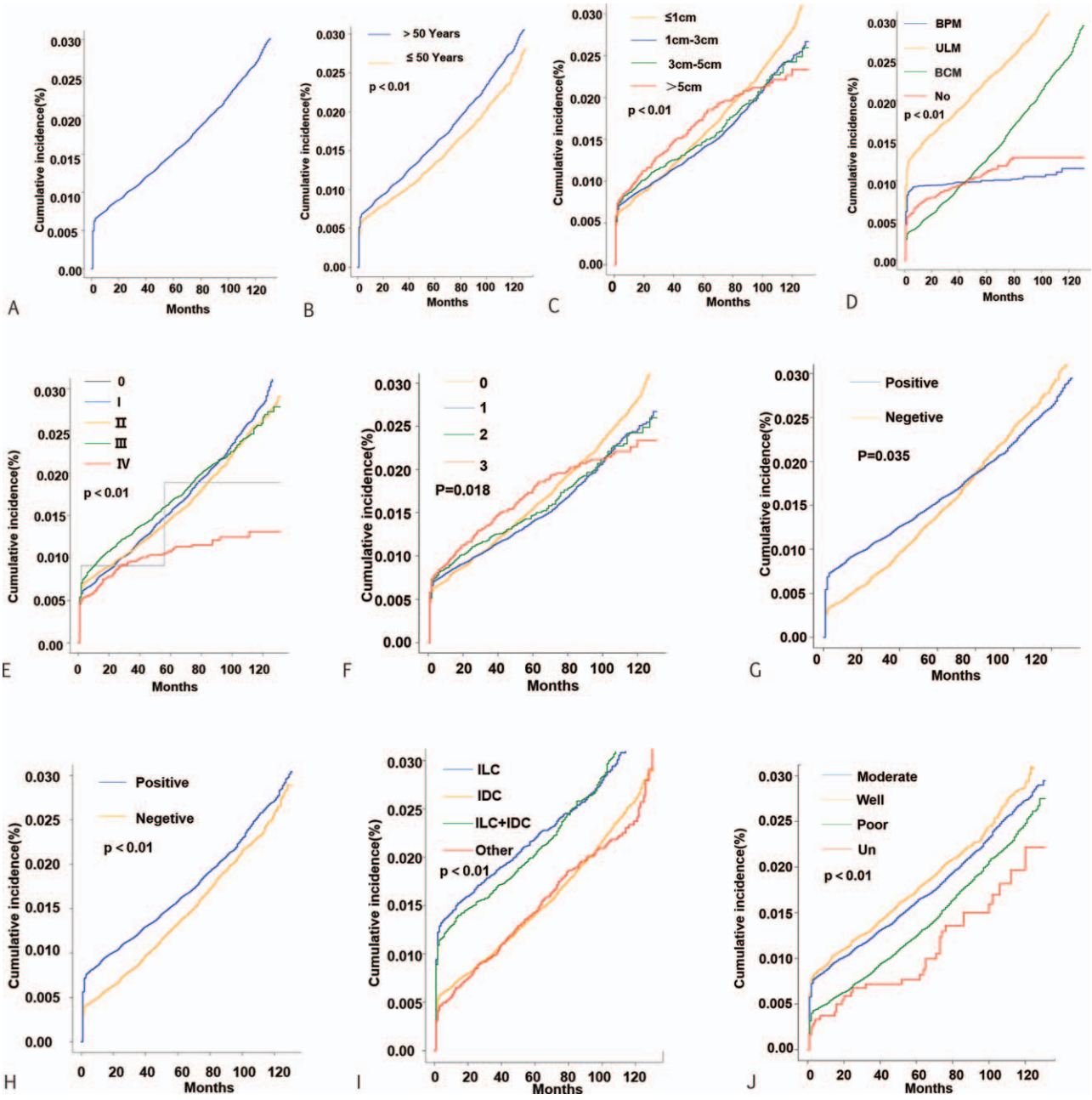

Figure 3. Cumulative incidence curves of CBC. (A) All, (B) age, (C) tumor size, (D) surgery, (E) stage, (F) number of lymph nodes, (G) ER status, (H) PR status, (I) histology, and (J) grade. ALL = all patients, CBC = contralateral breast cancer, mo = month.

addition, decision curve analysis was used to assess the clinical utility of the nomogram by compared with the all-screening and no-screening scenarios. Results showed that our model in a wide range of threshold probabilities (2%–3.5%) had larger clinical net benefit (Fig. 6).

4. Discussion

We screened a large cohort of 434,065 BC patients from the SEER database, of whom 6944 had developed CBC. We screened 7 independent risk factors from 9 potential risk contributors. We found that patients with ILC with a higher age at first diagnosis, smaller initial BC, better differentiation, ER-negative/PR-positive, and ULM were more likely to develop CBC. The surgical approach, degree of differentiation, histological type, and ER status contributed more to the development of CBC.

Subsequently, we created nomogram plots based on competing risk regression models to predict the risk of CBC in BC patients at 1, 5, and 10 years. Subsequent validation ensured the accuracy, stability and clinical usability of the model. To our knowledge, this is the first CBC prediction model built from such a large amount of patient information obtained from the SEER database. This model helps to reduce the limitations of traditional proportional regression analysis models on the results.

Table 2

Final hazard models of probability of contralateral breast cancer risk in breast cancer survivors among the cohort.

Factors	Category	Confidence	sHR(%)(95%CI)	*P* value
Age	≤50	−0.09812	0.907 (0.856 0.960)	<.001
Grade	Well	0.48956	1.632 (1.164 2.287)	.0045
	Moderate	0.37844	1.46 (1.044 2.042)	.027
	Poor	0.1816	1.199 (0.858 1.676)	.29
Stage	1	0.05466	1.056 (0.338 3.301)	.93
	2	0.01278	1.013 (0.324 3.168)	.98
	3	−0.04798	0.953 (0.302 3.010)	.93
	4	−0.3604	0.697 (0.219 2.222)	.54
Lymph node	0	0.0134	1.013 (0.852 1.205)	.88
	1	−0.08833	0.915 (0.778 1.077)	.29
	2	−0.09842	0.906 (0.778 1.056)	.21
Tumor size	1	−0.14214	0.868 (0.766 0.982)	.025
	2	−0.15546	0.856 (0.768 0.954)	.005
	3	−0.1437	0.866 (0.772 0.972)	.015
Surgery	ULM	0.62997	1.878 (1.593 2.213)	<.001
	CPM	−0.11284	0.893 (0.740 1.078)	.24
	BCM	0.05945	1.061 (0.899 1.252)	.48
ER status	Negative	0.30315	1.354 (1.240 1.479)	<.001
PR status	Negative	−0.22885	0.795 (0.739 0.857)	<.001
Histology	IDC	−0.31203	0.732 (0.672 0.797)	<.001
	ILC	−0.00132	0.999 (0.898 1.111)	.98
	Other	−0.3985	0.671 (0.591 0.762)	<.001

BCM = breast-conserving mastectomy, CBC = contralateral breast cancer, CI = confidence interval, CPM = contralateral prophylactic mastectomy, IDC = infiltrating duct carcinoma, ILC = infiltrating lobular carcinoma, moderate = moderately differentiated, poor = poor differentiated, sHR = subdistribution hazard ratio, tumor size: 1 = ≤1 cm, 2 = 1 to 3 cm, 3 = 3 to 5 cm, 4 = >5 cm, un = undifferentiated, ULM = unilateral mastectomy, well = well differentiated.

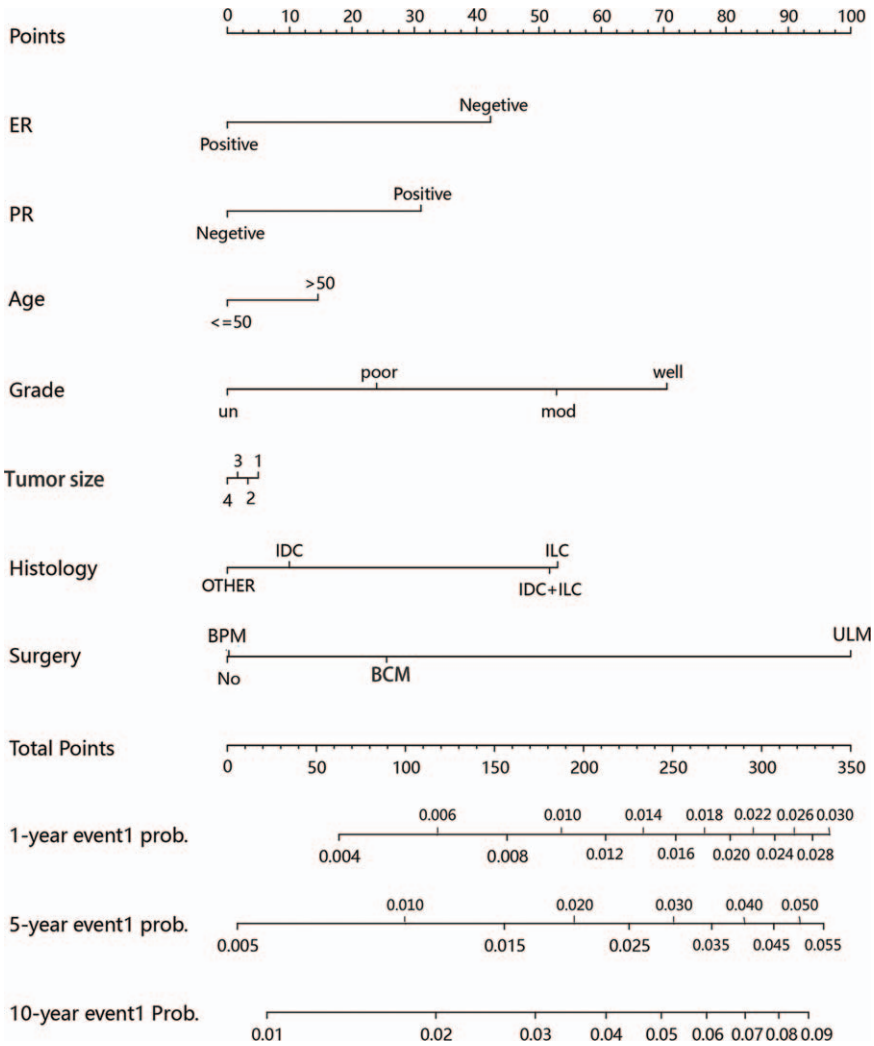

Figure 4. Competing risk nomogram for predicting 3, 5, and 10-year cumulative incidence of CBC in female patients with primary breast cancer.

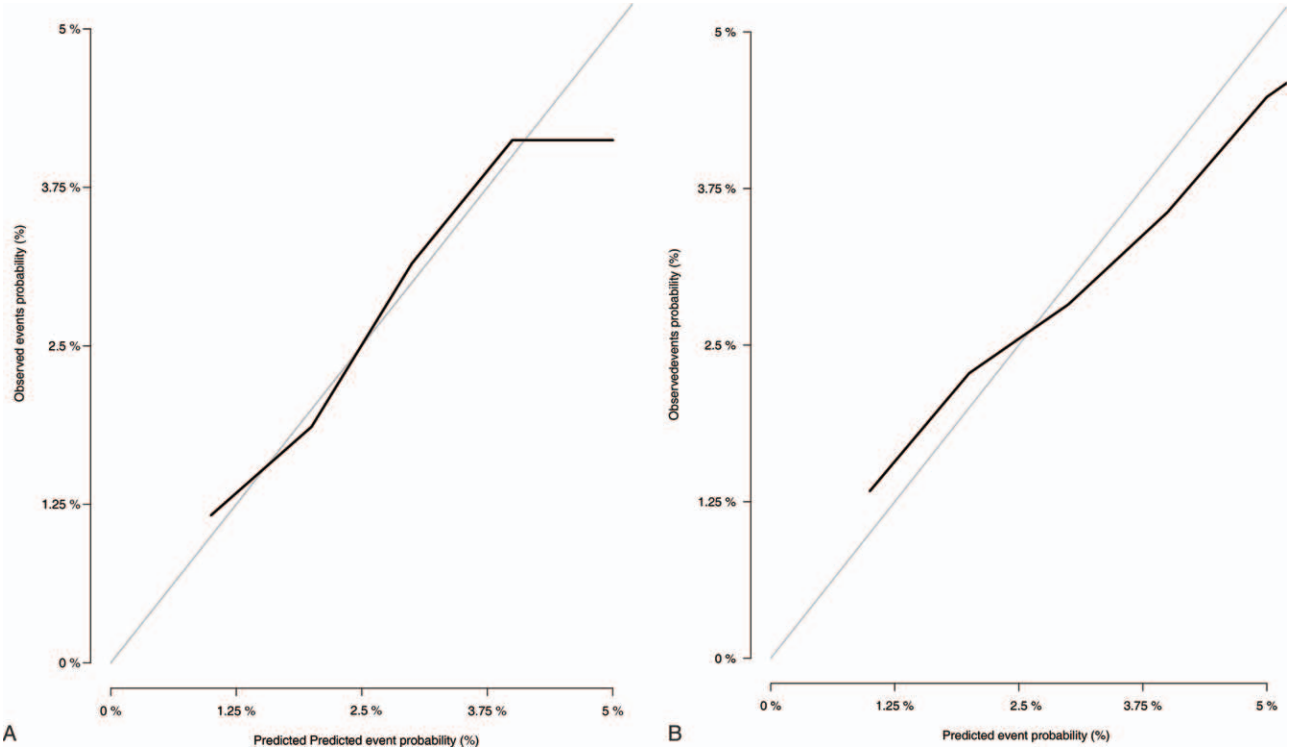

Figure 5. Calibration plot for internal validation of nomograms. The black solid line represents equality between the predicted and observed probability. The calibration plots for 5 years (A) and 10 years (B).

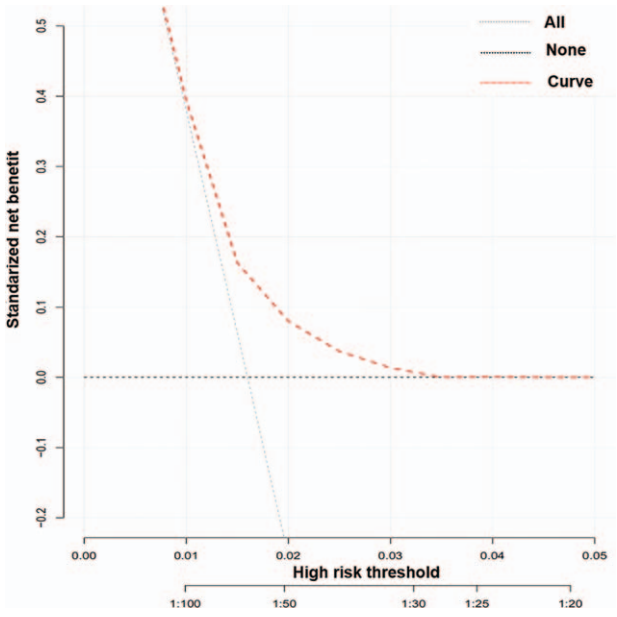

Figure 6. Decision curve analysis at 10 years for the CBC risk model. The x-axis is the threshold probability. The y-axis represents the net benefit for a given threshold probability. The dotted red curve represents the net benefit of the selection strategy based on prediction model for screening, compared with the net benefits in the alternative strategies of screening all patients (gray) and screening no patients (black).

Over the past decade, the competing risks model has gained popularity among medical researchers. The model has been gradually applied to prognostic studies for various malignancies, showing its advantages in dealing with competing events.[20] If the follow-up period is short or the competing risk is low, the difference between the traditional survival analysis method and the competing risk method may not be significant. When the proportion of individuals with competing risk is equal to or greater than the proportion of individuals with the endpoint event of interest, or the follow-up period is longer than 5 years, however, disregarding the competing risk leads to a decrease in the accuracy and testing of the competing event rate and significant bias in the results. In studies with competing risks, using competing events as truncated data and calculating the cumulative incidence rate using traditional survival analysis can lead to results that are greater than the cumulative incidence rate calculated using the competing risks model, overestimating the actual situation and leading to biased statistical results.[21]

In our study, the occurrence of CBC was the event of interest and death was the competing event. The death of BC patients from the cancer itself was the dominant competing event. Even though the incidence of CBC is increasing year by year,[22] there is still a non-negligible gap between the incidence of CBC compared to the mortality rate of BC. Therefore, the traditional comparative risk model would no longer be applicable. For this reason, we chose the competing risk model. We established a cumulative risk model based on the potential risk factors of CBC, which greatly reduces the bias that occurs in traditional survival analysis

models, makes the model results more realistic, and ensures the usefulness of the model through a series of validations.

Our study found a significantly reduced risk of CBC with CPM compared with BCM alone, whereas patients who underwent ULM had a significantly increased risk. This is similar to the results of Kurian et al,[23] but we studied the surgical approach more closely. Both BCM and CPM reduced the risk of CBC compared to ULM. We also included patients who had not had surgery and found that the risk of CBC was lower compared to those who underwent surgery. One possible explanation is that missed surgical opportunities due to late staging resulted in patients facing a higher mortality rate, thus hindering the development of CBC. Another explanation is that this group of patients underwent more comprehensive screening or more aggressive systemic therapy, which reduced the occurrence of CBC.

It is still controversial whether ILC is a potential risk for the occurrence of CBC. Langlands et al[24] found there was no significant difference between the occurrence and time to occurrence of CBC based on original cancer histology – 901 (2.8%) patients with IDC compared to 166 (3.1%) patients with ILC ($P=.169$), but de Glas et al[25] found that, although the absolute risk difference between ductal and lobular tumors was small, the incidence of CBC was highest in patients with lobular tumor morphology. This is consistent with our conclusion that there is an absolute elevated risk of developing CBC in cohorts with ILC or a mixture of both compared to IDC alone. Our results also found a higher risk of CBC in patients with ER-negative initial BC, which is consistent with the results of Reiner et al[26]: ER− first tumor status was associated with a 30% (95% confidence interval 1.1–1.6) increase in CBC risk compared to ER + first tumors. Tamoxifen use was not associated with a change in CBC incidence in ER+ patients. However, an analysis of the Stockholm Breast Cancer Registry,[27] which includes data on endocrine therapy but few other covariates, found no difference in CBC risk by ER status of the first tumor (ER+ standardized incidence ratio=2.30 vs 2.30 vs ER− standardized incidence ratio=2.17). Our study also found a greatly increased risk of CBC establishment with positive PR, contrary to the results of Reiner et al who concluded that women whose first primary tumor was PR− had a higher risk of CBC than women with PR+ disease.

In the age-specific CBC trend analysis, it was observed that the younger cohort faced more challenging conditions to develop CBC, compared to the older cohort. This is consistent with previous findings that women tend to have a higher risk of developing CBC when they are young at the time of the initial BC diagnosis.[28,29] However, the competitive risk model draws the contrary conclusion. The contradictory results of the 2 in the study are, we suspect, due to the different follow-up times of the 2 groups. de Glas et al[25] found that increasing age was associated with an increased risk of CBC within 6 months (subdistribution hazard ratio 2.34, 95% confidence interval 2.08–2.62, $P<.001$, patients aged 75 years and older compared to patients under 50 years). In contrast, after 6 months, the trend was reversed. Therefore, we conjecture that the incidence of CBC in elderly patients gradually decreases with increasing follow-up time. Our study also found better differentiation and smaller tumor size posed a potential risk for CBC, which is not in line with expectations. One possible reason is that patients with poorer differentiation or larger tumor size are often lost to treatment and increased BC mortality prevents CBC from occurring.

5. Limitations

Known BC susceptibility gene mutations BRCA1 and BRCA2 and a family history of BC are well-established risk factors for CBC. The lifetime risk of BC and of CBC for women who carry a BRCA mutation is very high.[30] Reiner et al have also demonstrated that women with a family history of BC have a higher risk of CBC even after a negative BRCA result. Unfortunately, the SEER database does not provide data on these important factors. Further research is also required on population-specific surveillance and screening strategies.

6. Conclusion

An increasing number of BC survivors are at risk of developing subsequent CBC. Therefore, it is important to determine which women are at risk. This study provides useful information on the risks of developing CBC based on a large population-based cohort. We developed a nomogram based on competing risk models to reliably predict the risk of developing CBC in BC survivors. Our findings may be useful for clinicians and carers in developing clinical counseling and risk-adapted long-term treatment for patients with BC.

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Author contributions

Conceptualization: Jiaci Tong.
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Formal analysis: Jiaci Tong.
Investigation: Jiaci Tong.
Methodology: Jiaci Tong, Dewei Tan.
Software: Jiaci Tong.
Supervision: Jing Ma, Ye Hu, Man Li.
Validation: Jiaci Tong.
Visualization: Jiaci Tong.
Writing – original draft: Jiaci Tong.
Writing – review & editing: Man Li.

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