Survival analysis for patients with metachronous contralateral breast cancer: Insights from a retrospective study

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Abstract. Continued advances in the diagnosis and treatment of breast cancer (BC) have led to an increase in the number of long-term BC survivors and an increase in the incidence of metachronous BC in the contralateral breast. Therefore, it is important to understand the factors that influence the development of metachronous BC; however, the impact of the laterality of the initial ipsilateral (I)BC as a risk factor for the development of metachronous contralateral (MC)BC has not been extensively investigated. The present study included 17,082 female patients with stage 0-3 IBC from the prospectively maintained Korean Breast Cancer Registry from 1989-2013 and divided them into two groups: Patients with MCBC (n=88) and those without MCBC (n=16,994). Risk factors that present at the initial BC diagnosis that could significantly influence the development of MCBC were screened for and risks were evaluated using the Fine-Gray subdistribution hazard model. Significant differences in baseline characteristics between MCBC and non-MCBC groups were demonstrated. Patients aged <40 years, those with histological and nuclear grade 3 tumors, and those with the triple-negative BC subtype were significantly more prevalent in the MCBC group than in the non-MCBC group. Additionally, the cumulative incidence of MCBC increased over time, with a notable increase from 0.1% in year 1 to 1.6% in year 10. Survival analysis revealed no significant differences in overall or BC-specific survival between the two groups. Key predictive factors identified for MCBC included an age of <40 years at initial diagnosis, a negative progesterone receptor status, and a Ki-67 score of >14%. Overall, the present study revealed several factors associated with MCBC and emphasized the need for long-term monitoring of BC survivors, considering these newly identified risk factors.

Introduction

With the ever-increasing incidence of breast cancer (BC) and improved diagnosis and treatment methods, BC survival rates are increasing, making it more likely that a woman will develop a second BC in the contralateral breast after completion of the initial treatment (1). Among patients with BC, contralateral (C)BC is the most common secondary cancer event, with an incidence of 0.5-1.0% per year (2,3). Several risk factors for CBC have been identified, including young age (2,4,5) and a family history of BC (5). Conversely, treatments, such as systemic adjuvant chemotherapy (6-8) and hormonal therapies, including tamoxifen or aromatase inhibitors, are known to reduce the risk of CBC (8,9).

Based on this understanding, the contralateral breast can be categorized into synchronous and metachronous (M)CBC. This classification stems from the report by Kilgore (10) on 'synchronous carcinoma' in 1921, which was later expanded by Haagensen and Rosato (11), who introduced temporal variance in bilateral BC. The distinction between synchronous and MCBC has been a subject of ongoing research, with time intervals for classification varying widely, such as 1 month (12,13), 3 months (14), 6 months (15) and 12 months (16-18). Most existing studies on the risk of metachronous CBC have relied predominantly on data from single institutions and notably, large-scale studies on Asian populations are scarce (14,17,18).

MCBC is a distinct pathological entity characterized by the development of a novel primary carcinoma in the opposite breast following the initial diagnosis. Contrary to synchronous tumors that are present in temporal proximity to the primary neoplasm, metachronous growths emerge after a lapse of time, marking them as separate oncogenic occurrences rather than as expansions or metastatic sequelae of the original cancer (19). The critical delineation between metachronous BC

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Abbreviations: BC, breast cancer; BCSS, BC-specific survival; BMI, body mass index; CBC, contralateral BC; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HRT, hormone replacement therapy; IBC, ipsilateral BC; LCIS, lobular carcinoma *in situ*; MCBC, metachronous contralateral BC; TNBC, triple-negative BC; OS, overall survival; PR, progesterone receptor; SHR, subdistributional hazard ratio; TNM, tumor-node-metastasis

Key words: MCBC, BCSS, Korean Breast Cancer Registry, BC laterality, competing risks analysis, bilateral BC

and metastatic spread is a profound consequence of clinical decision-making, with implications for treatment modalities and prognostic deliberations (20). Despite the challenges of confirming their etiological independence, MCBCs are widely acknowledged as *de novo* primary cancers, separate from the first occurrence. This understanding has a definitive bearing on surveillance, therapeutic stratification and prognostication in the continuum of care for survivors of BC (21). Considering the bilateral nature of the breast, extensive research has been performed on the laterality of BC, with studies demonstrating a higher incidence (22) and severity (23) of left-sided BC; however, studies extensively assessing the impact of the laterality of the initial ipsilateral BC as a risk factor for the development of MCBC are limited.

The present study used prospectively maintained clinical data from the Korean Breast Cancer Registry and aimed to assess the risk factors associated with the occurrence of MCBC. In this context, mortality is considered a competing factor in mitigating biases arising from deaths occurring before the development of MCBC (21). Furthermore, as MCBC allows for a clear delineation of primary and secondary cancers in a chronological sequence (22,23), the present study also aimed to evaluate whether the laterality of the initial ipsilateral (I)BC is a risk factor for the development of MCBC.

Materials and methods

Data source and study population. The present retrospective study was based on prospectively collected and maintained databases of patients who underwent BC surgery at 102 general hospitals. Female patients aged 18-79 years who were diagnosed with stage 0-3 BC by American Joint Committee on Cancer Tumor-Node-Metastasis staging (24) and underwent breast-conserving surgery or mastectomy as the primary breast surgery with curative intent between 1989-2013 were included in the present study. Patients who developed distant metastasis after the diagnosis of IBC but before the diagnosis of MCBC were excluded from the first step in determining eligibility. This is because metastatic BC, which may be indistinguishable from metachronous BC, was suspected in these circumstances. Patients without laterality data for initial IBC or MCBC, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 results, which are necessary immunohistochemistry data for molecular subtype classification, and those without stage results were excluded (Fig. 1).

Assessment. Patients who met the criteria were divided into MCBC and non-MCBC groups based on the development of MCBC. MCBC was defined as secondary contralateral BC diagnosed >12 months after the diagnosis of primary BC. The clinical characteristics of the patients included the following: Age at the time of primary cancer diagnosis; operation type (breast-conserving surgery or mastectomy); laterality of primary IBC; tumor-node-metastasis (TNM) stage; body mass index (BMI); parity; hormone replacement therapy (HRT) experience; histologic grade; nuclear grade; histological type; subtype; expression status of ER, PR and HER2; Ki-67 proliferation index; and history of chemotherapy, radiation therapy and hormone therapy.

The seventh edition criteria of the AJCC was used to classify the TNM staging (24). ER, PR and HER2 statuses were determined using immunohistochemistry as previously described (25). HER2 overexpression was defined as negative for immunohistochemistry grades 0-2+, whereas grade 3+ was considered positive. Patients with a grade of 1+ or 2+ underwent additional fluorescence *in situ* hybridization assessments as previously described (25). Based on ER, PR, HER2 and Ki-67 markers, tumors were grouped into five subtypes: Luminal A (ER^+ and/or PR^+, $HER2^-$ and Ki-67 <14.0%), Luminal B (positive for hormone receptors, $HER2^-$ and Ki-67 ≥14.0%), Luminal HER2 (positive for hormone receptors and $HER2^+$), HER2 amplified (ER^- and PR^-, but $HER2^+$), and triple-negative (TN)BC (ER^-, PR^- and $HER2^-$).

Statistical analysis. The clinical characteristics of the MCBC and non-MCBC groups were compared using the χ^2 and Fisher's exact tests. Kaplan-Meier analysis was used to compare the overall survival (OS) and BC-specific survival (BCSS) between the two groups, and the significance of the differences was assessed using the log-rank test. In addition, the Fine-Gray subdistributional hazard model was used to evaluate the risk factors for MCBC, considering patient mortality as a competing risk. In this context, 'time' was defined in a multifaceted manner to account for diverse clinical outcomes, representing the period from the date of IBC diagnosis to that of the occurrence of MCBC. For patients who died, 'time' spanned from their IBC diagnosis to the date of death. Where neither MCBC nor death occurred, 'time' was considered up to the last date on which the status of patient mortality and CBC occurrence was confirmed. This comprehensive approach allowed for a more delicate and precise assessment of MCBC risk over time, incorporating the critical aspects of patient mortality. This model included the following: Age; operation type; laterality; stage; BMI; delivery status; HRT; histological grade; nuclear grade; histological type; ER, PR, HER2 and Ki-67 status; and a history of radiotherapy, chemotherapy and hormone therapy. The model's assumption of proportional hazards was verified, and the fit of the model was assessed by calculating the P-values of the residuals. Statistical analyses were performed using the Statistical Package for Social Science version 29.0.1.0 (IBM Corp.) and R software version 4.3.0 (R Foundation for Statistical Computing). $P<0.05$ was considered to indicate a statistically significant difference.

Compliance with ethical standards. The study protocol was reviewed and approved by the Institutional Review Board of the Catholic University of Korea (Suwon, Republic of Korea; approval no. VC24ZISI0020) in accordance with the ethical guidelines of the Institutional and/or National Research Committee and the tenets of the 1964 Declaration of Helsinki and its later amendments. All the patient data were collected and maintained by the Korean Breast Cancer Society. All the patients provided written informed consent for the storage and use of their information for research purposes.

Results

Baseline characteristics. When comparing the proportions between the non-MCBC and MCBC groups using the χ^2 and

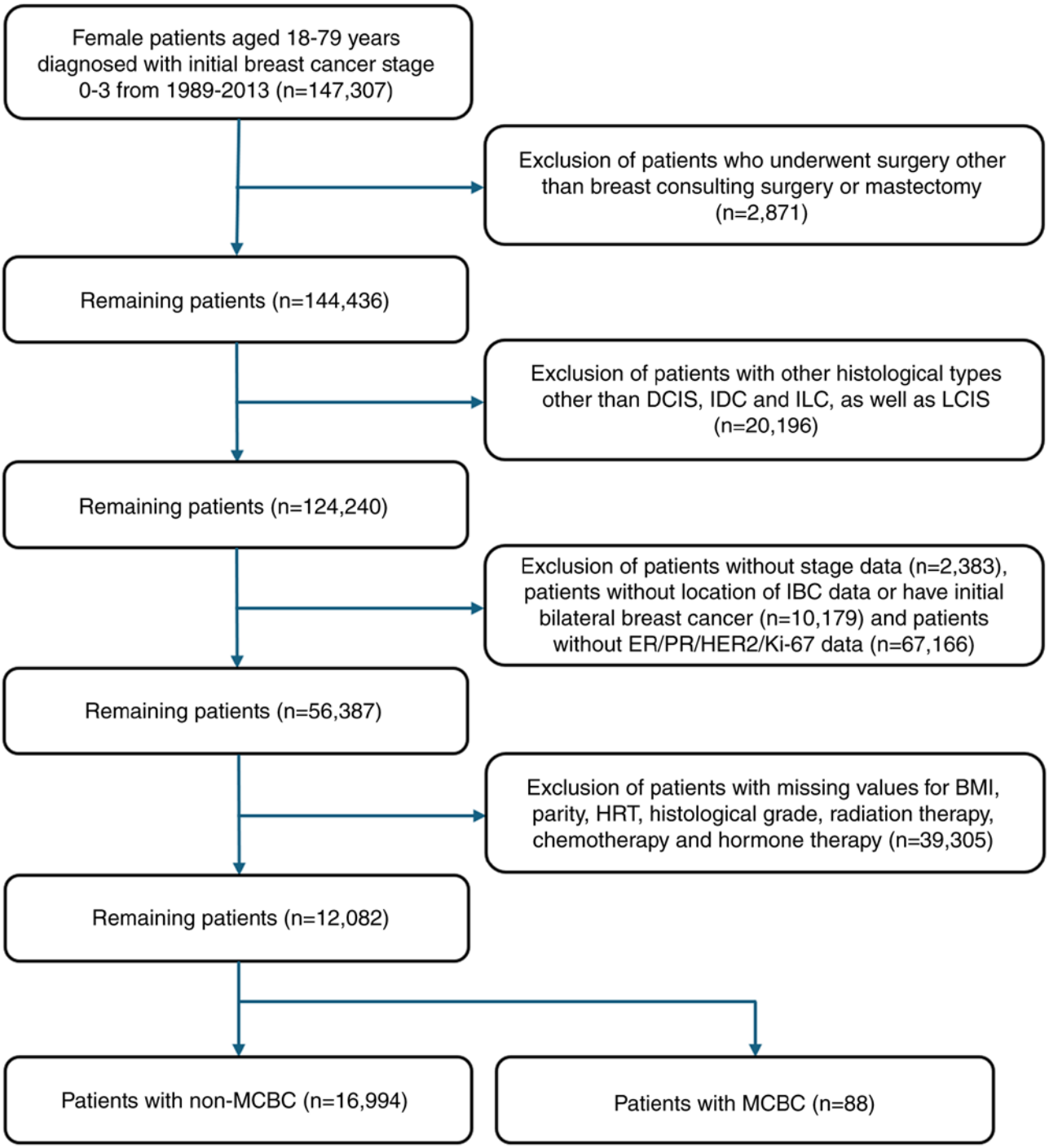

Figure 1. Consort diagram. DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma *in situ*; IBC, invasive breast cancer; HER2, human epidermal growth factor receptor 2; BMI, body mass index; HRT, hormone replacement therapy; MCBC, metachronous contralateral breast cancer.

Fisher's exact tests for baseline characteristics, the proportion of individuals <40 years of age was significantly higher in the MCBC group than in the non-MCBC group (14.9% vs. 31.8%; P<0.001). Significant differences were also observed in histological and nuclear grades, particularly in grade 3, where there was a significant difference in proportions between groups (38.4% vs. 52.3%; P=0.021 and 42.0% vs. 53.4%; P=0.016, respectively). Subtype distribution varied significantly between the non-MCBC and MCBC groups. Specifically, the Luminal A subtype occurred less frequently in the MCBC group compared with the non-MCBC group, and a greater proportion of TNBC was observed in the MCBC group relative to the non-MCBC group (34.4% vs. 20.5%; P=0.006 and 16.6% vs. 29.5%; P=0.006, respectively). Moreover, patients negative for both ER and PR were significantly more common in the MCBC group than in the non-MCBC group (30.8% vs. 47.7%; P=0.001 and 41.2% vs. 58.0%; P=0.001, respectively). Furthermore, patients with Ki-67 scores of ≥14% were significantly more prevalent in the MCBC group, with 56.0% in the non-MCBC group compared with 67.0% in the MCBC

group (P=0.038). Finally, a significantly higher proportion of patients did not receive hormonal therapy in the MCBC group compared with the non-MCBC group (30.1% vs. 42.0%; P=0.014; Table I).

Cumulative incidence. In the present study, the overall cumulative incidence of MCBC was assessed. The data indicated an incidence of 0.1% in the first year, which increased to 0.5% by the fifth year and further increased to 1.6% by the tenth year. These findings demonstrated a progressive increase in the risk of MCBC over time. The confidence intervals (CIs) at these time points were 0.0-0.1 for year 1, 0.3-0.7 for year 5, and 1.0-2.2 for year 10, which reflect the statistical variability of the estimates (Fig. 2).

Survival analysis. Survival outcomes were assessed using the Kaplan-Meier method, with the log-rank test used to evaluate the statistical significance between survival curves. At a median follow-up of 3.63 years, the log-rank test revealed no significant differences in OS or BCSS between the non-MCBC and MCBC cohorts (OS, P=0.23 and BCSS, P=0.56). The estimated 5-year OS rate was 94.7% in the non-MCBC group compared with 98.5% in the MCBC group, and the 10-year OS rates were 89.3 and 92.7%, respectively. For BCSS, the rates at 5 years were 98.3% in patients without MCBC and 100% in those with MCBC; at 10 years, the rates were 97.3 and 96.4%, respectively (Fig. 3).

Subdistributional Cox regression. To evaluate the determinants of the incidence of MCBC with death as a competing risk factor, a competing risk regression analysis was performed. The analysis indicated that patients aged ≤40 years had a significantly higher risk of developing MCBC compared with those who were >40 years. This was evidenced by a subdistributional hazard ratio (SHR) of 0.428 (95% CI, 0.223-0.819; P=0.010). Furthermore, a Ki-67 index of ≥14% significantly increased the risk of MCBC, with an SHR of 1.966 (95% CI, 1.053-3.668; P=0.034), indicating a pronounced susceptibility for MCBC in patients with elevated Ki-67 levels. Conversely, PR^+ was associated with a decreased risk of MCBC, with an SHR of 0.441 (95% CI, 0.203-0.956; P=0.038), suggesting a protective effect against MCBC development. Variables such as laterality, BMI and hormonal treatment of the initial BC were not significantly associated with the risk of MCBC. Moreover, the cancer stage at diagnosis did not significantly alter the risk profile of MCBC in this analysis. Treatment modalities, including radiation therapy, chemotherapy and hormone therapy, as well as histological and nuclear grades, ER status and HER2 status, did not demonstrate significant associations with MCBC risk (Table II).

Discussion

There is no universally established definition for metachronous BC. If a patient is diagnosed with IBC and subsequently develops contralateral BC, the criteria to determine whether it should be considered metachronous or metastatic BC are not clearly defined. When local recurrence or distant metastasis follows IBC, contralateral BC may be more likely to be classified as metastatic; however, in the absence of locoregional recurrence or distant metastasis, it is often regarded as metachronous BC (20,26). In cases where it is difficult to distinguish between metachronous BC and metachronous recurrence/occurrence, a comprehensive genetic analysis, such as next-generation sequencing using DNA extracted from primary and secondary BCs, is theoretically required. Nevertheless, as metachronous BC is considered to be increasing in frequency, but not absolutely, and as only longitudinal data from multiple institutions enable in-depth studies, tumor registry data, as used in the present research, remains the primary source, and extensive genetic analysis faces practical challenges. Encouragingly, recent research suggests that most bilateral BCs, including metachronous types, may not be genetically related in terms of clonal relationships, although this does not apply to all instances (20,26).

The present retrospective study aimed to elucidate risk factors associated with MCBC using data from the Korean Breast Cancer Registry. Upon analyses of baseline characteristics, it was observed that patients aged <40 years, with histological and nuclear grade 3 tumors, and the TNBC subtype, as well as patients negative for hormonal receptors (ER and PR), a Ki-67 index of ≥14%, and those who had not received adjuvant hormonal therapy, were present at a significantly higher proportion in the MCBC group than in the non-MCBC group. Conversely, variables such as the type of surgery performed, administration of systemic chemotherapy, stage of IBC and the status of HER2 did not demonstrate a significant difference between the MCBC and non-MCBC groups.

Furthermore, in the present study, IBC laterality demonstrated a preference for the left breast in both cohorts, with a higher, albeit not statistically significant, prevalence in the MCBC group compared with the non-MCBC group (51.3 vs. 56.8%; P=0.301; Table I). This finding aligns with that in the established literature suggesting a higher incidence of left-sided BC (22,27).

A detailed analysis of the cumulative incidence of MCBC was performed. The findings revealed a cumulative incidence of 0.1% at the end of the first year. This incidence gradually escalated, reaching 0.5% by the fifth year and further rising to 1.6% by the tenth year. These results not only delineate a progressive increase in the risk of MCBC over time but also indicate the importance of prolonged and vigilant monitoring. The confidence intervals, registering at 0.0-0.1 for the first year, 0.3-0.7 for the fifth year, and 1.0-2.2 for the tenth year, indicate the statistical variability inherent in the findings. This upward trajectory in incidence emphasizes the necessity for continuous surveillance of BC survivors, extending well beyond the initial decade post-diagnosis.

Contrary to previous research suggesting that patients with bilateral BC have a worse prognosis than those with unilateral disease (28), the analysis in the present study demonstrated no significant differences in the survival rates between patients with MCBC and those with non-MCBC. However, this is consistent with another Korean study (29), which also reported no notable survival differences between these groups, suggesting that improvements in treatment protocols, the importance of early detection, and possibly unique genetic or environmental factors within the Korean population may

Table I. Patient characteristics.

Characteristic	Non-metachronous BC (n=16,994)	Metachronous BC (n=88)	P-value
Age, years			<0.001
≤40	2,531 (14.9)	28 (31.8)	
>40	14,463 (85.1)	60 (68.2)	
Location of initial breast cancer (laterality)			0.301
Left	8,717 (51.3)	50 (56.8)	
Right	8,277 (48.7)	38 (43.2)	
Operation			0.352
BCS	10,478 (61.7)	50 (56.8)	
Mastectomy	6,516 (38.3)	38 (43.2)	
Stage			0.273
0	139 (0.8)	1 (1.1)	
1	7,708 (45.4)	46 (52.3)	
2	6,866 (40.4)	35 (39.8)	
3	2,281 (13.4)	6 (6.8)	
NAC			0.815
No	15,433 (90.8)	83 (94.3)	
Yes	1,561 (9.2)	5 (5.7)	
BMI, kg/m^2			0.249
<25	11,777 (69.3)	62 (70.5)	
≥25	5,217 (30.7)	26 (29.5)	
Parity			0.091
No	608 (3.6)	5 (5.7)	
Yes	16,386 (96.4)	83 (94.7)	
Oral contraceptive			0.091
No	14,566 (87.5)	70 (81.4)	
Yes	2,089 (12.5)	16 (18.6)	
HRT			0.954
No	15,419 (90.7)	80 (90.9)	
Yes	1,575 (9.3)	8 (9.1)	
Histological grade			0.021
1	2,402 (14.1)	12 (13.6)	
2	8,062 (47.4)	30 (34.1)	
3	6,530 (38.4)	46 (52.3)	
Nuclear grade			0.016
1	1,305 (7.7)	10 (11.4)	
2	8,550 (50.3)	31 (35.2)	
3	7,139 (42.0)	47 (53.4)	
Histological type			0.749
Ductal	16,485 (97.0)	85 (96.6)	
Lobular	509 (3.0)	3 (3.4)	
Lymphovascular invasion			0.116
No	9,347 (61.4)	52 (70.3)	
Yes	5,888 (38.6)	22 (29.7)	
Subtype			0.006
Luminal A	5,848 (34.4)	18 (20.5)	
Luminal B	4,271 (25.1)	20 (22.7)	
Luminal HER2	2,038 (12.0)	11 (12.5)	
HER2 amplified	2,018 (11.9)	13 (14.8)	
TNBC	1,819 (16.6)	26 (29.5)	

Table I. Continued.

Characteristic	Non-metachronous BC (n=16,994)	Metachronous BC (n=88)	P-value
Estrogen receptor			0.001
Negative	5,229 (30.8)	42 (47.7)	
Positive	11,765 (69.2)	46 (52.3)	
Progesterone receptor			0.001
Negative	7,002 (41.2)	51 (58.0)	
Positive	9,992 (58.8)	37 (42.0)	
HER2			0.455
Negative	12,938 (76.1)	64 (72.7)	
Positive	4,056 (23.9)	24 (27.3)	
Ki-67			0.038
<14%	7,472 (44.0)	29 (33.0)	
≥14%	9,522 (56.0)	59 (67.0)	
Radiation therapy			0.275
No	5,078 (29.9)	31 (35.2)	
Yes	11,916 (70.1)	57 (64.8)	
Chemotherapy			0.190
No	4,944 (29.1)	20 (22.7)	
Yes	12,050 (70.9)	68 (77.3)	
Hormonal therapy			0.014
No	5,107 (30.1)	37 (42.0)	
Yes	11,887 (69.9)	51 (58.0)	

Data are presented as n (%). BC, breast cancer; BCS, breast conserving surgery; NAC, neoadjuvant chemotherapy; BMI, body mass index; HRT, hormonal replacement therapy; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2.

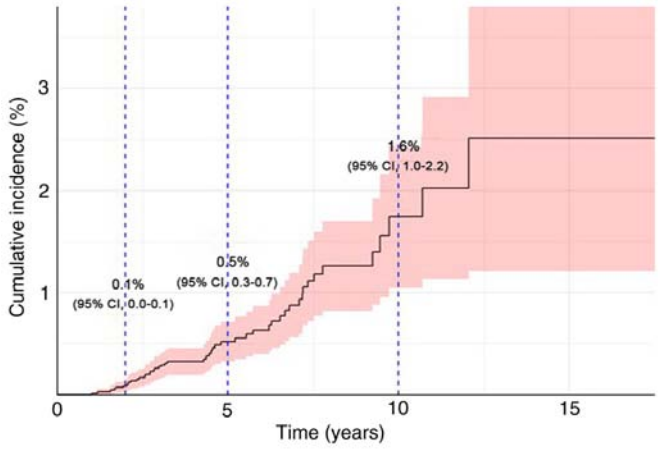

Figure 2. Overall cumulative incidence of metachronous contralateral breast cancer. CI, confidence interval.

contribute to diminishing the traditional survival gap between unilateral and bilateral BC cases. Nevertheless, it is not yet clear whether the findings of the present study are unique to the Korean population or whether they reflect global trends. To better understand these nuances, further research involving a broader international sample and the examination of additional variables, such as genetic markers, lifestyle impacts and health system differences, is required. Such research could reveal the extent to which these outcomes are influenced by regional characteristics and help to tailor BC treatment and survivorship planning on a global scale.

Moreover, the Fine-Gray subdistribution hazard model was applied to assess the risk factors for MCBC, considering mortality as a competing risk. This method was selected due to its ability to account for competing risks, thereby offering a more precise estimation of the incidence and impact of covariates over time (30,31). The results revealed that an age of ≤40 years at the time of IBC diagnosis, having a PR^- status, and having a Ki-67 score of ≥14% were significant risk factors for the onset of MCBC; however, the other variables assessed were not significant risk factors for MCBC. The current results align with the that of the existing literature that has identified a younger age at initial BC diagnosis as a risk factor for CBC (2,4,5) and highlights the significance of PR status and high Ki-67 scores in the context of MCBC risk (27,28). However, whilst in previous studies, chemotherapy and hormone therapy have been associated with a decrease in the incidence of CBC, the findings of the present study did not demonstrate significant evidence supporting this perspective (6-9). Moreover, during the data collection phase of the present study, ductal carcinoma *in situ* was classified as a ductal histological type, and lobular carcinoma *in situ* (LCIS) was not included as a lobular histological type. This decision reflects the current

Table II. Subdistributional Cox regression analysis.

Factor	HR	95% CI	P-value
Age, years			
≤40	-	-	-
>40	0.428	0.223-0.819	0.010
Location of initial breast cancer (laterality)			
Left	-	-	-
Right	1.020	0.590-1.759	0.936
Stage			
0	-	-	-
1	0.361	0.040-3.179	0.359
2	0.269	0.029-2.432	0.241
3	0.249	0.021-2.939	0.274
BMI, kg/m^2			
<25	-	-	-
≥25	1.097	0.588-2.042	0.772
Parity			
No	-	-	-
Yes	0.524	0.170-1.609	0.258
HRT			
No	-	-	-
Yes	1.793	0.761-4.221	0.180
Histological grade			
1	-	-	-
2	0.735	0.212-2.538	0.626
3	1.170	0.318-4.296	0.805
Nuclear grade			
1	-	-	-
2	0.515	0.154-1.712	0.279
3	0.507	0.129-1.983	0.334
Histological type			
Ductal	-	-	-
Lobular	2.002	0.257-15.540	0.510
Estrogen receptor			
Negative	-	-	-
Positive	0.709	0.305-1.646	0.421
Progesterone receptor			
Negative	-	-	-
Positive	0.441	0.203-0.956	0.038
HER2			
Negative	-	-	-
Positive	0.681	0.303-1.527	0.353
Ki-67			
<14%	-	-	-
≥14%	1.966	1.053-3.668	0.034
Radiation therapy			
No	-	-	-
Yes	1.257	0.352-4.477	0.718
Chemotherapy			
No	-	-	-
Yes	1.136	0.508-2.536	0.763
Hormonal therapy			
No	-	-	-
Yes	1.904	0.848-4.270	0.118

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HRT, hormonal replacement therapy; HER2, human epidermal growth factor receptor 2.

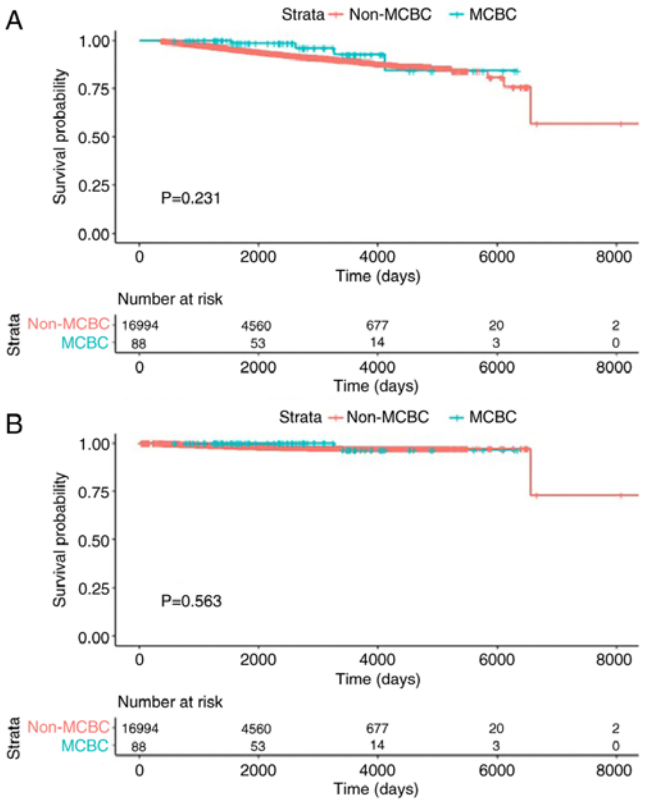

Figure 3. Overall survival and breast cancer-specific survival. Kaplan-Meier curves for (A) overall survival and (B) breast cancer-specific survival of patients with MCBC and non-MCBC. MCBC, metachronous contralateral breast cancer.

understanding that LCIS is not a form of cancer but is a risk factor for the development of BC. Consequently, patients with LCIS were excluded from the analysis. The results of the present study indicated that the histological type was not a significant risk factor for the development of MCBC, which is consistent with other studies that have also reported that the histological type does not constitute a risk factor for the occurrence of CBC (32,33).

Furthermore, whilst a PR$^-$ status was identified as a significant risk factor for the development of MCBC, ER status did not emerge as a significant risk factor in the Fine-Gray subdistribution hazard model. This distinction is noteworthy because it deviates from the common understanding that both hormone receptors typically serve a role in BC prognosis (27-29). Thus, the findings of the present study provide a new perspective

on the differential impacts of hormone receptor status on the risk of MCBC development. Potential reasons for the lack of significance of ER status in this context warrant further investigation and could help refine risk stratification and management in patients with IBC.

Family history is recognized as a risk factor for CBC (5); however, in the present study, it was not used as a variable due to the large number of missing values. For instance, of the 88 individuals in the MCBC group, only 11 had a known family history. Family histories of the remaining 77 patients were undocumented. Therefore, an association between family history and the occurrence of MCBC could not be ascertained. Future research may further explore this relationship, including an assessment of MCBC occurrence in patients with hereditary BC with BC gene (BRCA)1 and BRCA2 mutations.

The present study, which considered mortality as a competing factor, revealed the possible risk factors for MCBC. This methodology has enabled an in-depth understanding of the factors influencing the occurrence of MCBC, particularly the identification of PR^- status and high Ki-67 scores as new risk indicators. These findings offer a revised perspective on the management and monitoring of patients with BC.

The multivariate analysis indicated that the laterality of IBC is not a significant risk factor for MCBC; however, this finding does not diminish the relevance of laterality as a variable for future studies. It is conceivable that in subsequent studies involving diverse ethnic patient cohorts or using different research methodologies, consideration of IBC laterality may yield valuable insights. Therefore, laterality is worthy of careful consideration in future BC research.

Despite the insights provided by the present study, there are inherent limitations in its retrospective design. This approach is susceptible to missing data across parameters, accuracy challenges, and potential selection and information bias. Reliance on clinical records may hinder data standardization and introduce the risk of unaccounted-for confounding factors. Additionally, the ethnic and geographical homogeneity of the cohort constrains the broader applicability of the findings. Therefore, future research should endeavor to use prospective designs, encompass diverse populations, and implement rigorous standardization to enhance the robustness and generalizability of the outcomes.

Nonetheless, the present study offers significant insights into the risk factors for MCBC; however, these results should be approached with caution and regarded as the foundation for subsequent prospective investigations. Future studies should include broader demographics by incorporating patients from diverse ethnicities and regions, thereby expanding the sample range and enhancing the generalizability of the findings. Such studies, ideally encompassing larger and more varied cohorts and using prospective methodologies, are crucial to affirm the findings of the present study and extend their relevance and applicability across different clinical contexts and populations. The inclusion of varied ethnic and regional backgrounds in future research would help determine whether the identified risk factors are universally applicable or whether they exhibit variation among different groups. This expansion is vital not only for the validation of results but also for tailoring preventive strategies and interventions to address the specific needs of distinct populations.

In conclusion, the present comprehensive study on MCBC within the Korean population identified age, PR status and Ki-67 scores as significant risk factors but did not substantiate certain traditional views regarding histological types and therapy implications. Additionally, despite the limitations inherent to retrospective analyses, the findings suggest that bilateral BC does not inherently confer a worse prognosis than unilateral BC does in this demographic, indicating a potential shift in understanding the dynamics of BC progression and outcomes. Future research should focus on expanding these findings through prospective studies and broader international collaborations to confirm these observations and explore the impact of genetic, lifestyle and healthcare system factors on BC prognosis, ultimately contributing to targeted and effective patient care across diverse populations.

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Availability of data and materials

The data generated in the present study may be requested from the Korea Breast Cancer Society due to restrictions on the availability of these data, which were used under license for the current study, and so are not publicly available.

Authors' contributions

YJS designed and supervised the study and revised the manuscript. BKP analyzed the data from the Korean Breast Cancer Registry, and conceived and modified the manuscript. JS helped conceive the study, and drafted and modified the original manuscript. YJS and BKP confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present research received approval from the Institutional Review Board of the Catholic University of Korea (approval no. VC24ZISI0020). Written informed consent was obtained from all patients for the use and storage of their data in the present research.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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