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Contributing factors of contralateral breast cancer in patients with BRCA mutation (ON-BRCA II study, KoREa-BSG 11)

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Abstract

Background The cumulative risk of contralateral breast cancer (CBC) in BRCA1/2 carriers is remarkably higher than in non-carriers. This study aimed to investigate the clinicopathological predictors associated with the risk of metachronous CBC among breast cancer patients with BRCA1/2 mutations using correspondence analysis.

Methods This retrospective study included patients who underwent BRCA testing between January 2008 and December 2018. The inclusion criterion was patients being between 20 and 80-years-old with invasive breast cancer (pT1-3, N0-3). We performed univariate and multivariate survival analyses to assess the risks associated with BRCA mutations, and conducted correspondence analysis to identify contributing factors for CBC among subgroup by age and BRCA mutations.

Results Total of 4009 patients were included in this analysis. After median follow-up of 93 months, 278 cases of CBC were documented. Among 576 patients with BRCA mutations, there was no difference in the incidence of CBC between BRCA1 and BRCA2 carriers ($P = 0.07$). Correspondence analysis revealed that, in younger patients (< 50 years) with BRCA1 mutations, the triple-negative subtype (r = 0.93) and high grade (r = 0.74) showed the closest geometric proximity associated with CBC. In BRCA2 carriers, high Ki-67 labeling index (≥ 20%) demonstrated prominent geometric association in the biplot related to CBC, regardless of age (r = 0.93).

Conclusion Although no difference was found in the risk of CBC between BRCA 1/2 mutations, correspondence analysis revealed different contributing factors. For young BRCA carriers with a triple-negative subtype and poor pathologic parameters such as high grade and Ki-67 index, risk-reducing contralateral prophylactic mastectomy could be considered as a treatment strategy.

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Keywords Breast cancer, BRCA mutation, Prophylactic surgery, Prognostic factor

Introduction

Patients with breast cancer with BRCA1/2 mutations have a significantly higher cumulative risk of contralateral breast cancer (CBC) than non-carriers [1]. Previous studies have reported that the 10-year cumulative risk of CBC in BRCA1/2 carriers ranges from approximately 16–43%, whereas it is only 2.5% in non-carriers [2, 3]. Consequently, some patients with increased anxiety may opt for contralateral risk-reducing mastectomy (RRM) without an accurate assessment of their actual risk of CBC [4, 5]. However, it is suggested that for most patients with breast cancer and a low risk of CBC, RRM has no survival benefit [6]. Furthermore, RRM can have negative psychosocial effects, including adverse impacts on body image and social relationships [7].

Considering the high cumulative risk of CBC in BRCA1/2 carriers, identifying the contributing risk factors for CBC in patients with BRCA1/2 pathogenic variants is crucial to guide decisions regarding unilateral vs bilateral prophylactic mastectomies. However, data on the specific factors that influence the risk of CBC among BRCA1/2 mutation carriers remain limited. Therefore, this study aimed to distinguish BRCA1/2 carriers with a high cumulative risk of CBC, who may benefit from contralateral RRM, from those with a low risk of CBC, for whom unnecessary mastectomy could be avoided. Furthermore, we sought to evaluate prognostic differences, including CBC risk, among patients with breast cancer based on BRCA mutation status and investigate potential clinicopathological factors associated with CBC risk.

To comprehensively evaluate factors, we applied two complementary analytic approaches. Cox proportional hazards regression was used to estimate the magnitude and temporal effects of risk factors, whereas correspondence analysis was employed as an exploratory tool to visualize association patterns among categorical variables. These methods were designed to provide inferential and descriptive perspectives, respectively.

Materials and methods

Study populations and data collection

The ON-BRCA II is a multi-institutional cohort study conducted by the Korea Robot-Endoscopy Minimal Access Breast Surgery Study Group. Patients with primary breast cancer who underwent breast-conserving surgery or mastectomy and BRCA1/2 mutation testing between January 2008 and December 2018 were retrospectively identified from 14 institutions in South Korea.

The inclusion criteria were patients aged 20–80 years diagnosed with invasive breast cancer (pT1-3, N0-3). All enrolled patients underwent germline BRCA1/2 testing according to international guidelines, and were categorized as carriers or non-carriers based on pathogenic or likely pathogenic variants. BRCA1/2 testing was conducted either at the time of initial diagnosis or during postoperative follow-up, according to clinical indications and evolving national guidelines during the study period. The exclusion criteria were *de novo* metastatic disease, bilateral breast cancer at diagnosis, and pregnancy-associated breast cancer. In addition, individuals who underwent contralateral prophylactic mastectomy at the time of primary surgery were not included in the analysis of metachronous CBC, as no contralateral breast tissue remained at risk during follow-up.

All enrolled patients underwent mammography, breast ultrasonography, and magnetic resonance imaging both before and during surveillance. Surgical details, including the date of surgery as well as type of breast and axillary procedures conducted, were recorded. Various clinicopathological characteristics such as tumor size, lymph node (LN) metastasis, histological grade, hormone receptor status, and human epidermal growth factor receptor 2 (HER2) status were collected through medical chart review. Additionally, information on adjuvant treatments, including chemotherapy, hormone therapy, targeted therapy, and radiation therapy, has been documented. During the follow-up period, all instances of breast cancer recurrence, including locoregional recurrence, distant recurrence (DR), CBC, and mortality were recorded. The results of BRCA1/2 mutation tests were collected from all patients.

This study adhered to the Good Clinical Practice guidelines and principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Hanyang University Hospital (No. HYUH 2022-04-039). Owing to the retrospective study design, the IRB waived the requirement for written informed consent. The study was conducted in accordance with the STROCSS criteria.

Study variables

The primary prognostic outcomes of interest were the incidence of metachronous CBC, loco-regional recurrence, DR, and overall survival. BRCA mutation status was categorized into BRCA1, BRCA2, and non-carrier groups. Metachronous CBC was defined as "the occurrence of breast cancer in the contralateral breast more than one year after curative surgery for the primary breast cancer".

Among the demographic characteristics, age at surgery and family history were included in the analyses. Moreover, we considered the following treatment factors:

pathological information, surgical details, tumor size, LN metastasis, histological grade, Ki-67 labeling index (%), HR/HER2 status, risk-reducing bilateral salpingo-oophorectomy, radiation therapy, and neoadjuvant or adjuvant chemotherapy.

Statistical analysis

Frequency and χ2 test for independence

Frequency distributions by BRCA mutation status were obtained for discrete variables. To examine whether the frequency distribution of each demographic, pathologic, operational, and treatment-related variable was independent of BRCA mutation status, the χ^2 test was conducted.

Univariate and multivariate survival analyses

Differences in the survival probability among BRCA mutation status were examined using Kaplan–Meier analysis and the log-rank test. The overall log-rank test was followed by the Tukey–Kramer test, [8] which controlled for experiment-wise type I error rate, since three BRCA mutation status were under investigation. The cumulative hazard functions for BRCA mutation statuses were estimated using Kaplan–Meier analysis. To evaluate the effects of BRCA mutation status, both with and without adjusting for demographic, pathological, operational, and treatment-related variables, a Cox proportional hazards (PH) regression was conducted. The proportionality hazards assumption in the Cox PH model was evaluated for sensitivity analysis using interaction terms between each explanatory variable and the standardized survival time. The statistical significance of these terms was jointly tested, followed by individual Chi-square tests. All significant interaction terms were included in the final model to correctly interpret the time-varying effects of the covariates. Stratified Cox PH models were not attempted to avoid reduced sample sizes and the complications of inference from multiple stratified Cox regressions.

Correspondence analysis

Correspondence analysis is a nonparametric statistical method that uses count data to create a two-way stacked table by stacking the categories of multiple discrete variables [9]. It is a quantitative analysis method that visually displays the strength of associations between categories on a biplot, typically comprising two dimensions, to capture most total inertia, namely the total variability present in the input data matrix [10, 11]. The strength of the associations demonstrated on the two-dimensional space can also be quantified by calculating correlation values. Smaller angles between vectors indicate stronger associations.

For the correspondence analysis, four age-prognosis combined groups were formed: those without a relapse or incidence and aged under 50 (Group 1, n = 2846 for CBC; 2619 for recurrence; 2883 for death), those without a relapse or incidence and aged ≥50 (Group 2, n = 884 for CBC; 905 for recurrence; 934 for death), those with a relapse or incidence and aged under 50 (Group 3, n = 184 for CBC; 411 for recurrence; 147 for death), and those with a relapse or incidence and aged ≥50 (Group 4, n = 94 for CBC; 73 for recurrence; 44 for death). The four comparison groups are located in the rows, whereas the categories of the nine contextual variables are positioned in the columns of the input data matrix for the prognosis. In the biplot, the comparison groups are represented as points and categories of contextual variables are represented as vectors.

Statistical methods and software

Most statistical analyses were conducted using SAS (version 9.4 TS Level 1M7; SAS Institute, Inc.). Correspondence analysis was performed using R Studio (version 2024.04.1+748) and R software (version 4.4.0). The R code provided directly by the corresponding author of a previous study[12] was modified to fit our data.

Results

Baseline characteristics of the study participants

Data from a multi-year retrospective study (2008–2018) comprising records of 352 individuals with BRCA1 mutations, 224 with BRCA2 mutations, and 3433 non-carriers were used. Approximately 76% of patients with breast cancer who participated in this study were under 50 years of age. Significant differences were noted among BRCA mutation statuses in the baseline characteristics, including age, family history of breast cancer within three degrees of kinship, molecular subtypes, KI-67 labeling index, LN metastasis, and histological grade. Treatment factors, such as risk-reducing bilateral salpingo-oophorectomy (BSO), chemotherapy, and radiation therapy, differed between subgroups according to the BRCA mutation status (Table 1).

Effects of BRCA mutations on survival outcomes

Kaplan–Meier analysis and log-rank test

Among the three prognoses investigated, only metachronous CBC differed significantly in the overall log-rank test. The subsequent Tukey–Kramer test on CBC for multiple comparisons demonstrated that both BRCA1 and BRCA2 mutation statuses differed from the non-carrier status regarding survival probabilities, with no significant difference observed between the BRCA1 and BRCA2 mutations (P = 0.07, Table 2). During median follow-up of 93 months, 278 cases of CBC occurred. The cumulative incidence rates of CBC at 10 years after surgery were 4.4% in non-carrier and 7.8% in BRCA carrier, specifically 9.1% for BRCA1 and 5.8% for BRCA2 carriers.

Table 1 Characteristics of 4008 study participants by BRCA mutation status

Variables (abbreviations)	Non-carrier		BRCA1 carrier		BRCA2 carrier		*P* value[a]
	n(%)	*n*	*n*(%)	*n*	*n*(%)	*n*	
Age		3432		352		224	< 0.001
<50	2577(75.1)		295(83.8)		158(70.5)		
≥50	855(24.9)		57(16.2)		66(29.5)		
Family history of breast cancer within three degrees of kinship (hb)		2715		296		188	< 0.001
No	1278(47.1)		109(36.8)		39(20.7)		
Yes	1437(52.9)		187(63.2)		149(79.3)		
Risk-reducing BSO[b]		3432		352		224	< 0.001
No	3379(98.5)		289(82.1)		152(67.9)		
Yes	53(1.5)		63(17.9)		72(32.1)		
Molecular subtypes		3321		348		218	< 0.001
HR + /HER2-	2018(60.8)		102(29.3)		172(78.9)		
HER2 +	730(22.0)		26(7.5)		14(6.4)		
TNBC	573(17.3)		220(63.2)		32(14.7)		
KI-67 labelling index		3433		352		224	< 0.001
<20%	3201(93.2)		302(85.8)		190(84.8)		
≥20%	232(6.8)		50(14.2)		34(15.2)		
Pathological tumor size		3383		350		220	0.48
≤20 mm	2172(64.2)		215(61.4)		136(61.8)		
>20 mm	1211(35.8)		135(38.6)		84(38.2)		
Lymph nodes metastasis		3399		351	220		< 0.001
Negative	2305(67.8)		260(74.1)		128(58.2)		
Positive	1094(32.2)		91(25.9)		92(41.8)		
Histological grade		3211		321		218	0.001
I or II	2128(66.3)		100(31.2)		132(60.6)		
III	1083(33.7)		221(68.8)		86(39.4)		
Surgery type		3433		352		223	0.02
Breast-conserving surgery	2125(61.9)		244(69.3)		135(60.5)		
Mastectomy	1308(38.1)		108(30.7)		88(39.5)		
Chemotherapy		3404		351		223	0.001
No	1270(37.3)		61(17.4)		60(26.9)		
Yes	2134(62.7)		290(82.6)		163(73.1)		
Radiation therapy		3413		351		223	0.01
No	901(26.4)		74(21.1)		43(19.3)		
Yes	2512(73.6)		277(78.9)		180(80.7)		
Metachronous CBC[c]		3433		352		224	0.001
No	3226(94.0)		306(86.9)		198(88.4)		
Yes	207(6.0)		46(13.1)		26(11.6)		
Any disease recurrence		3433		352		224	0.38
No	3023(88.1)		302(85.8)		200(89.3)		
Yes	410(11.9)		50(14.2)		24(10.7)		
Death		3433		352		224	0.09
No	3278(95.5)		327(92.9)		213(95.1)		
Yes	155(4.5)		25(7.1)		11(4.9)		

[a]The *P* value for each pair of categorical variables was obtained using the χ^2 test for independence

[b]Bilateral salpingo-oophorectomy

[c]Contralateral breast cancer

Table 2 Univariate analysis according to BRCA mutation status on survival outcomes

Comparison	Risk of CBC			Recurrence			Death		
	χ^2	*P* value[a]	*P* value[b]	χ^2	*P* value[a]	*P* value[b]	χ^2	*P* value[a]	*P* value[b]
BRCA1 carrier vs Non-carrier	17.73	< 0.001	< 0.001	2.19	0.33	0.77	3.52	0.17	0.22
BRCA2 carrier vs Non-carrier			0.01			0.95			0.75
BRCA1 carrier vs BRCA2 carrier			0.07			0.30			0.26

[a]The *P* value was obtained using the log-rank test for comparing survival probability distributions across different BRCA mutation statuses

[b]The *P* value for each pair of BRCA mutation statuses was obtained from pairwise comparisons using the Tukey–Kramer test, conducted after a significant result from the overall log-rank test, controlling for the experiment-wise type 1 error rate

Note. CBC: Metachronous contralateral breast cancer

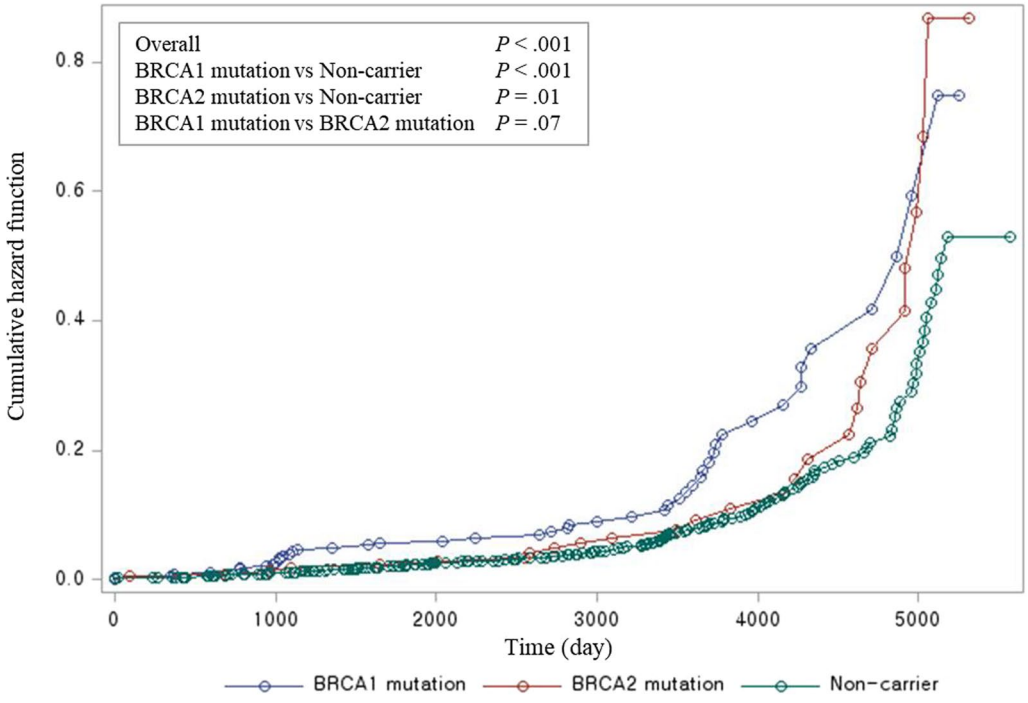

Fig. 1 Cumulative hazard functions for metachronous contralateral breast cancer according to BRCA mutation status. Blue: BRCA1 carriers; Red: BRCA2 carriers; Green: non-carriers

The estimated cumulative hazard functions for the three BRCA mutation statuses are shown in Fig. 1.

Cox proportional hazards regression

Differences in the survival probability regarding the risks of CBC, recurrence, and death among patients with different BRCA mutation statuses were explored using Cox proportional hazards regression with and without contextual factors. Cause-specific hazard models were used to estimate the effects of predictors on instantaneous risk, given the relatively low incidences of the competing risks (5%–12%). The joint test evaluating all interaction terms collectively was significant in every risk analysis. Consistent with the univariate analysis results, the groups differed only in the risk of metachronous CBC. Both the BRCA1 and BRCA2 mutation groups, as opposed to the non-carrier group, revealed a significantly higher risk of metachronous CBC when contextual factors were considered (Table 3). Additionally, 5 of the 11 covariates included in the final adjusted regression model for CBC showed significant interaction effects, indicating that the covariates have time-varying effects. For instance, the hazard ratio for the KI-67 labeling index (≥20%) increased with each 1 standard deviation above the mean follow-up time, whereas the hazard ratios for histological grade III, chemotherapy, radiation therapy, and treatment type (mastectomy) decreased. In contrast, risk-reducing BSO, the HER2+ molecular subtype and older age consistently appeared as risk factors over time, while family history of breast cancer remained a protective factor for CBC. For recurrence, positive lymph node metastasis remained a persistent risk factor over time. All six time-varying covariates were risk factors early on and became protective later in time. For death, the KI-67 labelling index (≥20%), positive lymph node metastasis, and histological grade III were constant risk factors

Table 3 Risk of CBC, recurrence, and death from the Cox regression analysis

Predictor variables (Reference category)	CBC		Recurrence		Death	
	Estimate ($\hat{\beta}$)	Hazard ratio [95% CI]	Estimate ($\hat{\beta}$)	Hazard ratio [95% CI]	Estimate ($\hat{\beta}$)	Hazard ratio [95% CI]
Mutation type (Non-carrier)[a]						
BRCA1	0.66	1.94[1.41–2.67]	0.16	1.17[0.87–1.57]	0.40	1.49[0.97–2.27]
BRCA2	0.30	1.35[0.89–2.03]	−0.20	0.82[0.54–1.24]	−0.05	0.96[0.52–1.76]
Mutation type (Non-carrier)[b]						
BRCA1	0.85	2.34[1.53–3.59]	0.18	1.20[0.85–1.70]	0.22	1.24[0.70–2.21]
BRCA2	0.82	2.28[1.31–3.97]	0.24	1.27[0.81–2.01]	0.07	1.07[0.49–2.33]
Age (<50 years) ≥50 years	0.53	1.70[1.21–2.39]	−0.24	0.78[0.59–1.04]	0.15	1.17[0.75–1.81]
Family history of breast cancer (No) Yes	−0.38	0.69[0.49–0.96]	−0.83	0.44[0.30–0.63]	0.13	1.14[0.75–1.71]
Risk-reducing BSO[c] (No) Yes	0.83	2.29[1.36–3.85]	0.15	1.17[0.65–2.10]	−0.43	0.65[0.20–2.16]
Molecular classification (HR + /HER2-)						
HER2 +	0.61	1.84[1.19–2.85]	−0.52	0.59[0.34–1.05]	−2.00	0.14[0.04–0.46]
TNBC	0.42	1.53[0.97–2.40]	−0.85	0.43[0.22–0.84]	−0.54	0.58[0.28–1.21]
KI-67 labelling index (>20%) ≥20%	−0.15	0.86[0.29–2.56]	0.16	1.17[0.64–2.15]	1.13	3.09[1.52–6.30]
Pathologic tumor size (≤20 mm) > 20 mm	0.08	1.08[0.76–1.53]	0.19	1.21[0.96–1.53]	1.00	2.73[1.55–4.82]
Lymph node metastasis (Negative) Positive	−0.16	0.85[0.58–1.25]	0.46	1.58[1.24–2.02]	0.85	2.34[1.48–3.67]
Histological grade (I or II) III	0.00	1.00[0.69–1.45]	−0.28	0.76[0.48–1.20]	0.49	1.63[1.05–2.54]
Chemotherapy (No) Yes	0.03	1.03[0.67–1.57]	−0.34	0.71[0.45–1.13]	6.38	592.69[70.72–4966.90]
Radiation therapy (No) Yes	−0.41	0.66[0.37–1.18]	−2.25	0.11[0.07–0.16]	−0.25	0.78[0.42–1.47]
Surgery type (Breast-conserving therapy) Mastectomy	−1.40	0.25[0.16–0.39]	−2.06	0.13[0.08–0.20]	−0.08	0.92[0.60–1.42]
(Family history of breast cancer: Yes) X (Survival time) interaction			−0.58	0.56[0.44–0.72]		
(Molecular classification: HER2 +) X (Survival time) interaction			−0.60	0.55[0.37–0.83]	−1.80	0.17[0.07–0.42]
(Molecular classification: TNBC) X (Survival time) interaction			−0.79	0.45[0.29–0.71]	−1.04	0.36[0.19–0.66]
(KI-67 labelling index: ≥20%) X (Survival time) interaction	0.75	2.13[1.04–4.34]				
(Pathologic tumor size: > 20 mm) X (Survival time) interaction					0.36	1.44[0.97–2.12]
(Histological grade: III) X (Survival time) interaction	−0.41	0.67[0.51–0.86]	−0.35	0.70[0.51–0.96]		
(Chemotherapy: Yes) X (Survival time) interaction	−0.44	0.64[0.47–0.89]	−3.17	0.04[0.02–0.07]	−7.22	0.00[0.00–0.00]
(Radiation therapy: Yes) X (Survival time) interaction	−2.36	0.09[0.07–0.14]	−1.78	0.17[0.12–0.23]	−1.03	0.36[0.21–0.62]
(Surgery type: Mastectomy) X (Survival time) interaction	−1.38	0.25[0.19–0.34]	−1.55	0.21[0.16–0.28]		

[a]The statistics were obtained from the unadjusted Cox proportional hazards regression analysis

[b]The statistics were obtained from the adjusted Cox proportional hazards regression analysis

[c]Bilateral salpingo-oophorectomy

CBC Metachronous contralateral breast cancer

over time. Four covariates exhibited time-varying effects. The HER2+ and TNBC molecular subtypes, chemotherapy, and radiation therapy began as risk factors early on and became protective later in time. Pathologic tumor size (>20 mm) was a risk factor, and its associated risk increased significantly over time. Because death was rare (4.76%), the model used highly imbalanced data, producing extreme confidence intervals for chemotherapy terms.

Correspondence analysis for the risk of CBC

For the correspondence analysis, the four age–prognosis groups were defined as follows: Group 1 (G1): patients <50 years without CBC; Group 2 (G2): ≥50 years without CBC; Group 3 (G3): <50 years with CBC; Group 4

Table 4 Contributing categories of contextual variables in the biplot for contralateral breast cancer

BRCA1 carriers		**BRCA2 carriers**		**Non-carriers**	
(72% + 21% = 94%)[a]		(58% + 27% = 85%)[a]		(75% + 21% = 96%)[a]	
Category	Contribution[b]	Category	Contribution[b]	Category	Contributionb
Grade I/II	15.6	Grade III	13.3	Family history	43.1
HR + /HER2-	13.8	Ki-67 ≥20%	11.3	Without family history	14.5
HER2 +	13.2	Grade I/II	9.6	No chemotherapy	5.8
No chemotherapy	11.4	Node metastasis	8.9	HER2 +	5.1
TNBC	10.7	Tumor size > 2 cm	6.6		
Grade III	10.0				
No radiotherapy	5.4				
Mean:	4.93		4.47		5.05

[a]The quantities represent the percentages of the total inertia explained by the first and second dimensions, and their combined sum

[b]Pooled contribution to the two-dimensional biplot

Table 5 Pearson correlations between age-contralateral breast cancer combined groups and categories of contextual variables with substantial contributions

BRCA1 carriers						
	HR + /HER2-	HER2 +	TNBC	Grade III	No chemotherapy	No radiotherapy
Group 1	0.82	−0.56	−0.21	−0.97	0.30	−0.63
Group 2	0.79	0.62	−1	−0.53	1.00	0.54
Group 3	−0.93	−0.39	0.93	0.74	−0.96	−0.3
Group 4	−0.28	0.96	−0.45	0.6	0.37	0.98
BRCA2 carriers						
	Ki-67 ≥ 20%	**Tumor size > 2 cm**		**Node metastasis**		**Grade III**
Group 1	−0.71	−0.34		0.82		−0.95
Group 2	0.45	0.62		−0.60		1.00
Group 3	0.99	−0.30		−1.00		0.56
Group 4	0.99	−0.32		−1.00		0.54
Non-carriers						
	Family history		**HER2 +**		**No chemotherapy**	
Group 1	−0.91		−0.56		−0.68	
Group 2	0.97		0.41		0.54	
Group 3	−0.93		0.21		0.06	
Group 4	−0.39		0.85		0.76	

Group 1 (n=2,846): patients aged<50 years without contralateral breast cancer

Group 2 (n = 884): Patients aged ≥50 years without contralateral breast cancer

Group 3 (n = 184): patients aged < 50 years with contralateral breast cancer

Group 4 (n = 94): Patients aged ≥50 years with contralateral breast cancer

(G4): ≥50 years with CBC. These groups were analyzed against key clinicopathologic variables to identify associations contributing to CBC risk. Stratified analysis was conducted for each BRCA mutation status to further examine the associations between the four combined groups and all the categories of the nine contextual variables. This stratification underscored on the risk of CBC as the three BRCA statuses differed significantly in their CBC survival probabilities. Two-dimensional biplots from the correspondence analysis accounted for most total inertia, specifically 94%, 85%, and 96% for BRCA1 carriers, BRCA2 carriers, and non-carriers, respectively (Table 4). Table 5 lists the Pearson correlations between the combined groups and categories of contextual variables that made substantial contributions. The following interpretation primarily highlighted on the associations with an absolute correlation value of ≥0.70 for the contextual variables that contributed above the mean pooled contribution to the two-dimensional biplot.

Regarding patients with BRCA1 mutations, Group 4 showed a strong correlation with HER2+ (r = 0.96), whereas Group 3 was highly correlated with TNBC (r = 0.93). Histologic grade III was more likely to be associated with the two groups with CBC, whereas histologic grade I/II was associated with the groups without CBC, particularly in Group 1. The correlation coefficient was 0.94. Group 2 showed a very strong positive correlation with not receiving chemotherapy, whereas Group 3 exhibited a very strong negative correlation with this category, indicating a strong positive association with

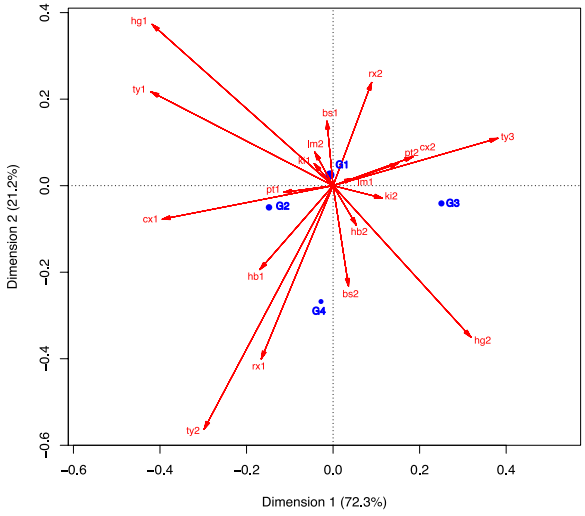

Fig. 2 Correspondence analysis biplot among BRCA1 carriers for metachronous contralateral breast cancer

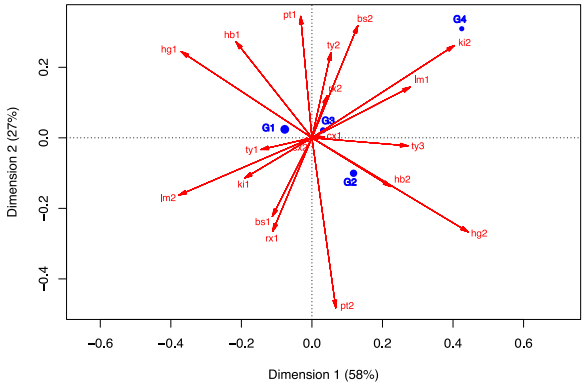

Fig. 3 BRCA2 mutation group's biplot for metachronous contralateral breast cancer

chemotherapy. Group 4 was strongly correlated with the absence of radiation therapy.

Among individuals with a BRCA2 mutation, the groups with CBC (Groups 3 and 4) showed the closest geometric proximity with a KI-67 level of ≥ 20% and an absence of LN metastasis. The correlation coefficients were close to 1.00. In the groups without CBC, Group 1 demonstrated a strong correlation with histological grades I/II, whereas Group 2 was associated with histological grade III. A pathological tumor size of ≥ 20 mm showed the closest geometric proximity with the older group without CBC than with any other group, although the association was of moderate magnitude ($r = 0.62$). Group 1 was also associated with the presence of LN metastasis ($r = 0.82$) and showed a negative association with the KI-67 index of ≥ 20%, indicating an association with a level below 20% ($r = -0.71$).

Among non-carriers, the presence of a family history of breast cancer within three degrees of kinship demonstrated prominent geometric association in the biplot

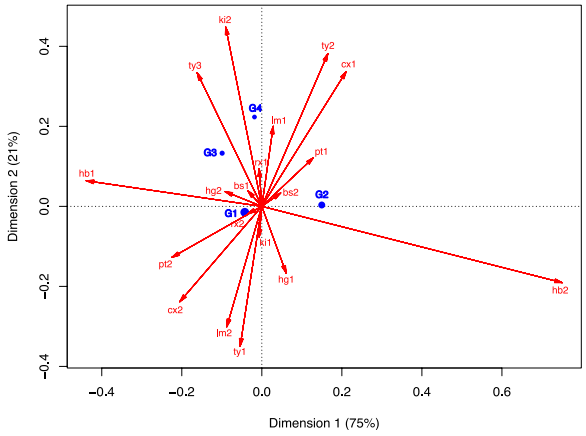

Fig. 4 Non-carrier group's biplot for metachronous contralateral breast cancer. G1: < 50 years, no CBC (n = 2,846), G2: ≥50 years, no CBC (n = 884), G3: < 50 years, with CBC (n = 184), G4: ≥50 years, with CBC (n = 94). Variable categories: bs1 or bs2 = No/Yes for risk-reducing BSO, cx1 or cx2 = No/Yes for chemotherapy, hb1 or hb2 = No/Yes family history within three degrees, hg1 or hg2 = histologic grade I-II / III, ki1 or ki2 = KI-67 < 20% / ≥20%, lm1 or lm2 = LN metastasis negative / positive, pt1 or pt2 = Tumor size ≤20 mm / > 20 mm, rx1 or rx2 = No/Yes for radiation therapy, ty1/ty2/ty3 = HR + /HER2-, HER2 + , TNBC subtypes

with older age without CBC (Group 2; $r = 0.97$). Conversely, the absence of such a history was associated with Group 3 ($r = 0.89$), while Group 4 was associated with the HER2+ subtype ($r = 0.85$) and without chemotherapy ($r = 0.76$).

The associations were presented as two-dimensional biplots. Figure 2 displays a biplot for the BRCA1 mutation status, whereas the biplots for the other statuses are presented in Figs. 3 and 4. On each biplot, the categories of the contextual variables that contributed substantially to the plot solution and were strongly correlated with the comparison group appeared as long vectors with small angles to the group. For instance, in Fig. 2, TNBC (ty3) and histologic grade III (hg2) stood out near the younger group with the CBC (G3). Notably, the estimated correlations did not necessarily match 100% with the visual inspection results. In the biplot, multidimensional categorical variables were aggregated into a two-dimensional space, and correlation estimation was based on a two-dimensional space.

Discussion

This study examined the potential clinical factors contributing to the risk of CBC in patients with breast cancer with BRCA1/2 pathogenic mutations using two complementary analytic approaches. Cox proportional hazards regression provided inferential estimates of relative risk over time and allowed assessment of time-varying effects under a model-based framework. In contrast, correspondence analysis visually represented association structures among categorical variables in

a reduced-dimensional space. Using correspondence analysis, we sought to deepen our understanding of the detailed connections between several contextual factors and prognostic outcomes according to the BRCA mutation status. Our results confirm that BRCA1/2 mutation carriers have a significantly higher risk of metachronous CBC than non-carriers, which is consistent with previous studies [13–15]. Notably, CBC risk did not differ significantly between BRCA1 and BRCA2 carriers, indicating that both mutations confer similar risks of susceptibility to CBC. Furthermore, we identified key clinicopathological factors that influence CBC risk, which may help refine risk stratification and guide optimal treatment decisions for BRCA1/2 mutation carriers. The strong associations identified in the correspondence analysis (e.g., TNBC and high-grade disease in younger BRCA1 carriers) indicate subgroups with distinctly elevated CBC risk, and these findings may support more proactive consideration of contralateral risk-reducing mastectomy, whereas patients without these features may be managed with surveillance rather than prophylactic surgery.

Several clinicopathological factors are significantly associated with the risk of CBC. Patients aged ≥50 years exhibited a constant risk over time of developing CBC, which differs from prior research indicating a higher CBC risk among younger BRCA mutation carriers [16]. Van den Broek et al reported that 10-year cumulative CBC risk showed ranges of 24–31% before age 40 years and 8% to 21% after 40 years, respectively. [17] Several factors may account for this discrepancy. First, residual confounding cannot be excluded, as certain clinical variables known to influence CBC risk (such as oophorectomy timing, adjuvant endocrine therapy duration, and surveillance intensity) were not consistently captured across institutions. Second, cohort effects and generational differences in treatment practices may have contributed; older carriers in our dataset were treated under earlier standards of care with potentially less consistent access to tailored surveillance. Third, unmeasured non-genetic factors or differences in tumor biology across age groups may also have influenced the observed pattern. Further research is warranted to clarify the relationship between age at diagnosis and risk of CBC in BRCA1/2 carriers.

Regarding molecular subtypes, the TNBC subtype was a constant risk factor over time for CBC, and in a stratified analysis the HER2-positive and TNBC subtypes are more frequently linked to the risk of CBC, particularly among BRCA1 carriers. This finding is consistent with prior research demonstrating that TNBC, which is strongly associated with BRCA1 mutations, is more aggressive and carries a higher risk of recurrence and contralateral disease [18]. Histologic grade was another important pathologic factor influencing CBC risk. High-grade (histological grade III) tumors are more commonly associated with CBC, particularly in younger patients with BRCA1 mutations. This supports the hypothesis that tumor biology is instrumental to CBC risk and highlights the importance of incorporating histopathological features into CBC risk assessment.

In this study, risk-reducing BSO were also a constant risk factor over time for CBC, although it was not among the variables that contributed substantially to the biplot solutions. While BSO does reduce the risk of primary breast cancer in BRCA1/2 carriers, its effect on the risk of CBC remain controversial [19]. The association between risk-reducing BSO and increased CBC risk in our results may be explained by selection bias, as patients at higher perceived genetic or familial risk risk were more likely to undergo BSO in real-world practice. Therefore, the result should be understood within the context of clinical decision patterns rather than as evidence of a harmful effect of BSO. Because participating institutions did not use a single unified protocol for risk-reducing BSO, decision were made according to internationally accepted criteria combined with individualized clinical judgment and patient preference. According to NCCN (National Comprehensive Cancer Network) guideline, risk-reducing BSO is strongly recommended for BRCA1 carriers between ages 35–40 and for BRCA2 carriers between ages 40–45, after completion of childbearing, because of the substantially elevated lifetime risk of ovarian, fallopian tube, and primary peritoneal cancer [20]. The guidelines further emphasize consideration of earlier surgery for individuals with a strong family history of early-onset ovarian cancer or when clinical judgment suggests higher risk.

The median follow-up duration in our cohort was 93 months. While this represents a reasonably long observation period, it may not be sufficient to fully delineate long-term CBC risk, particularly for BRCA2 carriers. Previous large-scale prospective studies have shown that BRCA2-associated CBC risk often increases gradually and becomes more apparent over extended follow-up periods beyond 10–15 years. [2, 14] In our data, the relatively small difference in cumulative CBC incidence between BRCA2 carriers and non-carriers at later time points (as illustrated in Fig. 1) may therefore reflect limited temporal observation rather than true biological equivalence. Residual risk could continue to emerge with longer surveillance, and caution is warranted when interpreting these late estimates. Extended longitudinal follow-up or validation in datasets with longer observation periods would be valuable for accurately characterizing late-onset CBC risk among BRCA2 mutation carriers.

The findings of the present study have important clinical implications. Considering the substantial risk of CBC in BRCA1/2 carriers, personalized risk stratification

is essential for optimizing surgical decision-making. Although contralateral RRM may be beneficial for high-risk patients, our results indicate that not all BRCA1/2 carriers require RRM, particularly those with low-risk clinicopathologic features [21, 22]. Overuse may result in unnecessary surgery, leading to potential adverse effects on body image, psychological well-being, and quality of life [23, 24]. Our correspondence analysis highlights that certain clinicopathologic features—such as triple-negative subtype and high-grade tumors in younger BRCA1 carriers, or high Ki-67 index in BRCA2 carriers—correspond to distinctly higher CBC risk. In contrast, carriers without these high-risk characteristics may fall into an intermediate-risk group for whom the benefit of contralateral RRM is less clear. For these individuals, a tailored approach that incorporates age, tumor biology, Ki-67 status, and patient values may help avoid unnecessary prophylactic surgery while ensuring adequate surveillance. By integrating these risk markers into clinical discussions, clinicians can provide more individualized counseling that aligns preventive strategies with each patient's specific risk profile and preference. Developing personalized CBC risk models that incorporate genetic, pathological, and clinical factors may enhance patient outcomes by enabling more targeted preventive strategies [25].

Correspondence analysis, stratified by BRCA mutation status, produced both visual and quantitative outcomes, providing richer information about the associations at the categorical levels of the variables under investigation. Under the framework of Cox proportional hazards regression, the detailed associations at the categorical levels could be achieved by incorporating multiple interaction effects. However, the inclusion of such effects could lead to quasi-complete separation due to a lack of data points in some or many of the possible combined cells of the model. Results affected by the quasi-complete separation issue are questionable. Although interaction terms among explanatory variables could not be incorporated, we were able to include interactions with survival time to determine which actors exhibited constant risk or protective effects over time and to assess time-varying effects for factors with inconsistent patterns. This study used Cox PH regression to identify covariates whose effects on the hazard were either time-invariant or time-varying, thereby formally characterizing departures from the proportional hazards assumption. In parallel, correspondence analysis was employed to examine and visualize associations between age–prognosis combinations and the individual categories of each covariate. These two analytic approaches serve complementary purposes rather than functioning as substitutes. Cox PH regression provides an inferential, model-based assessment of covariate effects on event risk over time, whereas correspondence analysis offers a geometric, multivariate depiction of how categorical covariate levels co-occur with distinct age–prognosis profiles in the observed data space. Together, the combination of model-based inference and exploratory geometric representation yields a more nuanced understanding of the underlying associations than either approach alone.

Despite the strengths of our study, including its large, multi-institutional cohort and robust statistical analyses, some limitations should be acknowledged. First, the retrospective nature of the study introduces a potential selection bias, and reliance on medical record data, including family history and social habits, may affect data insufficiency. Second, we did not account for lifestyle and environmental factors, such as reproductive history and hormonal exposure, which could influence the risk of CBC [26]. In the correspondence analysis for non-carriers, an unexpected pattern emerged: the presence of a family history of breast cancer clustered with older patients who did not develop CBC, whereas younger patients who developed CBC tended to report no family history. Older cohorts may exhibit higher awareness or more complete reporting of family history compared with younger patients, reflecting possible cohort or generational differences in documentation. In addition, non-genetic contributors - including lifestyle, reproductive factors, or treatment-related exposures - may play a relatively larger role in CBC development among younger non-carriers. Future research incorporating comprehensive risk factors, including genomic profiling and lifestyle influences, is needed for the development of risk prediction models. Third, correspondence analysis is inherently descriptive and emphasizes visual exploration of association structure rather than formal hypothesis testing or statistical inference. Distances and proximities in biplot maps reflect relative association patterns within the sample and should not be interpreted as effect sizes or measures of statistical significance. Consequently, findings from correspondence analysis should be viewed as exploratory and hypothesis-generating, providing insight into the configuration and direction of associations that can inform, but not by themselves establish, generalizable conclusions. Fourth, the clinicopathologic features strongly associated with CBC risk in BRCA1 carriers - younger age (<50 years), TNBC subtype, and high histologic grade - align closely with the well-known biologic profile. Because these characteristics are highly prevalent among BRCA1 carriers in real-world settings, they may offer limited discriminatory value for refining individualized decisions regarding prophylactic contralateral mastectomy. Rather than redefining risk categories, our findings contextualize how these established biologic characteristics continue to dominate CBC risk in real-world clinical settings. This reinforces the clinical relevance of integrating known tumor biology into

individualized risk assessment and surgical decision-making. For BRCA2 carriers, we have to acknowledge that Ki-67 assessment is known to show substantial inter-observer and inter-laboratory variability, and uniform assessment was not feasible in this retrospective multi-center cohort without centralized pathology review. In our cohort, differences in scoring methods and reporting thresholds across institutions may have influenced this result. Several participating institutions used semi-quantitative or categorical reporting systems, particularly in earlier years of the study period, which tended to underestimate proliferation when later converted to unified thresholds. As a result, this association should be considered hypothesis-generating and warrants validation in larger, prospective cohorts with standardized Ki-67 evaluation.

In conclusion, although no difference in the risk of CBC between BRCA 1 and BRCA 2 mutations was detected, different contributing factors were identified through a correspondence analysis. These findings provide potential clues for personalized risk assessment and emphasize the importance of individualized surgical decision making. To validate these findings and optimize risk-reducing strategies for patients with breast cancer with BRCA1/2 mutations, further prospective studies are needed.

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Data availability
Research data that support the findings of this study are securely stored in an institutional repository and are available to share from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Hanyang University Hospital (No. HYUH 2022–04-039) and followed the principles of the Declaration of Helsinki, which protects human subjects in medical research. Owing to the retrospective study design, the IRB waived the requirement for written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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