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EPIDEMIOLOGY

Age-related risk factors associated with primary contralateral breast cancer among younger women versus older women

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Abstract

Purpose Contralateral prophylactic mastectomy is increasing, despite unclear evidence of improving survival. To investigate the age-related risk factors for contralateral breast cancer (CBC).

Methods This study included 8716 patients diagnosed with non-metastatic unilateral invasive breast cancer between 1989 and 2008. Data on primary tumor size, node metastasis, grade and subtype using individual matching were used to adjust for differences in the primary tumor and treatment between younger and older age groups. CBC risk factors, CBC-free survival, and annual CBC risk were analyzed by age.

Results The younger group included 652 patients aged under 35 years, and the older group included 2608 women aged 35 years or older. The median time to CBC development was 6.1 years. CBC was detected in 6.6% of the women in the younger group and 2.5% of those in the older group. Multivariable analysis revealed a relative CBC risk of 2.48 in younger women compared to older women. The risk was significantly higher among women with human epidermal growth factor receptor 2 (HER2)-overexpressing tumors (hazard ratio [HR] 4.98), a family history of breast cancer (HR 7.79), and anti-hormone therapy (HR 3.46). In younger women with HER2-positive cancer, CBC occurrence peaked at 4.6 years after surgery, in those with hormone receptor-positive cancer, it peaked at 7.1 years after surgery, and in triple-negative disease cases, and it increased steadily over time.

Conclusions After adjusting for primary breast tumor characteristics, patients < 35 years old had 2.5 times the risk of CBC development compared to the older women. CBC occurrence peaked within 5 years after primary breast cancer in younger women with the HER2-positive subtype and after 5 years in cases with the hormone receptor-positive subtype.

Keywords Young breast cancer · Contralateral breast cancer · HER2/neu · Metachronous

Introduction

About 1–4% of primary breast cancer patients develop contralateral breast cancer (CBC) [1–5]. Younger age at the first diagnosis of breast cancer, family history of breast cancer, BRCA mutations, large tumor size, lymph node involvement, lobular type, negative hormone receptor status, and

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not having undergone hormone therapy or chemotherapy are associated with an increased risk of CBC [2–12]. A particularly relevant risk factor for CBC development is young age at primary cancer diagnosis [1, 2, 10, 13–15]. Kurian et al. [2] reported that women diagnosed with the disease before the age of 30 years had a 36-fold higher risk of CBC than expected. Similarly, a variety of studies have shown that younger age groups present a considerably elevated CBC risk, ranging from 2- to 36-fold [1, 8, 10, 13–15].

Previous research suggests that the higher CBC risk in younger women is associated with genetic factors, including family history and BRCA mutations, high levels of the triple-negative subtype, and aggressive characteristics of the first tumor [10–12, 16]. Verhoog et al. [11] found that BRCA1 mutation carriers with an onset age lower than 50 years had a 40% CBC occurrence rate, whereas those with an onset age higher than 50 years had a 12% rate.

The use of contralateral prophylactic mastectomy (CPM) is increasing [17], although its benefits on survival are still under debate. While CPM is reported to enhance survival in some high-risk populations,[18, 19], a recent study with 496,488 breast cancer patients reported no improvement in survival after CPM [17]. A larger proportion of younger women undergo this procedure than older women and, overall, its use has been increasing with time [17, 20]. Identifying the risk factors for CBC at a younger age may help reduce CPM rates, through a decrease in CBC incidence.

The aim of this study was to determine the risk factors for CBC and the associated risk rate (incidence in a certain time frame) in younger and older women using a matched cohort adjusted for several factors likely to influence CBC development.

Patients and methods

This retrospective cohort study included a total of 9633 consecutive patients, diagnosed with first invasive breast cancer at the Asan Medical Center, from January 1, 1989, to December 31, 2008. Detailed information on the Asan Medical Database has been previously reported [21]. Of them, 917 patients were excluded due to the presentation of bilateral breast cancer, carcinoma in situ, unknown subtype, or metastatic breast cancer (stage IV) at first diagnosis. A total of 8716 patients were enrolled and divided into two groups based on age: 674 patients were aged younger than 35 years and 8042 were aged 35 years or older. To adjust for potential confounding factors, we performed individual score matching using a greedy algorithm, in which randomly selected individuals in the younger group (< 35 years old) were paired with comparable individuals in the older (control) group (≥ 35 years old) who fulfilled the matching criteria. Four controls per case were selected based on tumor stage, lymph node metastasis, histologic grade, and subtype. Finally, a total of 652 and 2608 patients were included in the younger and older groups, respectively. Analyzed data included patients' age, tumor and treatment characteristics including tumor recurrence, CBC occurrence, and CBC risk factors. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Tumor subtypes were defined according to the hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2) status, as assessed by immunohistochemistry, and included the following four categories: HR-positive/HER2-negative (HR+/HER2−), HR-positive/HER2-positive (HR+/HER2+), HR-negative/HER2-positive (HR−/HER2+), and HR-negative/HER2-negative (HR−/HER2−). HR-positivity was defined as a tumor cell staining strength of 1% or higher, or an Allred score ranging from 3 to 8 based on immunohistochemistry staining. If either the estrogen receptor or progesterone receptor showed positivity, the case was classified as HR-positive, whereas when both markers showed negativity, the case was classified as HR-negative. Tumors of 1 or 0 grade were considered HER2-negative, whereas grade 3 tumors were considered HER2-positive. When the HER2 grade was 2 by immunohistochemistry, either silver-enhanced in situ hybridization or fluorescence in situ hybridization was performed and HER2 amplification was defined as positive.

Contralateral breast cancer was defined as the time from surgery to the first appearance of recurrence in the contralateral breast. To clearly distinguish a second primary CBC from a synchronous CBC, the CBC was defined as a primary event if it was diagnosed 6 months or later after the initial breast cancer, with a follow-up through to May 2017. Cancer-specific survival was defined as the time from the first breast cancer surgery to death.

This study was approved by the Asan Medical Center review board, which waived the need for informed consent (IRB No. 2017-0586).

Statistical analysis

Women who were alive at the end of the study period, lost to follow-up, or who died of other causes were censored at the date of their last observation. All statistical analyses were performed using SPSS Statistics version 21 (SPSS Inc., Chicago, IL, USA) and R 3.4.0. Categorical variables were compared using a two-sided Chi-squared test, and continuous variables were compared using an independent sample *t* test. A two-sided $P < 0.05$ was considered statistically significant. Age-adjusted hazard ratios and 95% confidence intervals (CIs) were compared using Cox models with robust standard errors that accounted for the clustering of matched pairs. The adjusted hazard ratio considered family history,

body mass index, chemotherapy, and hormone therapy. CBC-free survival and hazard curves were estimated using the Kaplan–Meier and kernel-based methods, respectively.

Results

Patient characteristics

Cohort matching according to T stage, node metastasis, grade, and subtype by age resulted in 652 individuals in the younger group (< 35 years old) and 2,608 in the control group (≥ 35 years old). The clinicopathologic characteristics of the study cohort are summarized in Table 1. The median age at primary breast cancer diagnosis was 32 years in the younger group and 47 years in the older group. The median follow-up durations were 131 and 128 months for the younger and older groups, respectively, and both groups had a similar family history, type of surgery, and radiotherapy. The older patients were likelier to be overweight than the younger patients (88.9% vs 97.0%, $P < 0.001$). Those in the younger group differed from those in the older group in that they presented a lower occurrence rate of lobular type cancer (2.3% versus 0.6%), were likelier to have undergone treatment with chemotherapy (73.1% versus 85.0%), and were less likely to have received endocrine therapy (64.1% versus 58.4%). Among patients receiving hormone therapy, all those under age 35 years received tamoxifen ($n = 381$) and 31 of them received GnRH agonists (8.1%, $n = 31/381$). In patients aged older than 35 years, 90.2% received tamoxifen and 9.8% received aromatase inhibitors ($n = 1508$ versus 163, respectively). Of the patients receiving tamoxifen, 11.6% received GnRH agonists ($n = 174/1508$).

Overall, CBC was detected in a total of 108 (3.3%) patients, and the median time to CBC development was 6.1 years in each group. There were no significant differences in the pathological features between the CBC and first cancer (Table 2).

CBC rates according to intrinsic subtype

Among the 652 younger women, 43 developed CBC, with a 10-year cumulative incidence of 6.1% (95% CI 4.0–8.1%); among the 2,608 older women, 65 developed CBC, with a 10-year cumulative incidence of 2.3% (95% CI 1.7–3.0%). Subgroup analysis according to the intrinsic subtype revealed that for all subtypes the CBC rate was significantly higher in the younger than older women, and that the triple-negative subtype was associated with a higher CBC incidence than the other subtypes. Younger and older women with the triple-negative subtype had 10-year cumulative CBC incidence rates of 9.7% and 5.0% (95% CI 4.7–14.6% and 3.2–6.9%), respectively. The 10-year CBC rate in younger patients with HER2 overexpression was 7.2% (95% CI 1.2–13.2%), while that among older patients was slightly lower (1.5%; 95% CI 0.1–2.8%) (Fig. 1, eTable 1).

Multivariable analysis of CBC incidence

Multivariable analysis adjusted by family history, chemotherapy, hormone therapy, and body mass index revealed that the risk of CBC was higher in the younger (hazard ratio 2.48; 95% CI 1.70–3.63) than older patients, and subgroup analysis identified younger age as an independent risk factor for all subtypes (Fig. 2, eTable 3). Younger patients with HER2-overexpressing tumors had a fivefold higher risk relative to older women, regardless of HR status (hazard ratio 5.29 in HR + HER2+; hazard ratio 4.95 in HR−/HER2+; Fig. 2).

Compared to the older women, the younger patients treated with endocrine therapy for primary tumors had a 3.5-fold (95% CI 1.88–6.35) higher CBC risk; those without endocrine therapy had a 1.8-fold (95% CI 1.13–3.01) higher CBC risk. Younger patients with a first- and/or second-degree family history were at a significantly greater CBC risk than older patients with a family history (hazard ratio 7.79; 95% CI 2.44–24.85).

Annual risk of CBC

Both groups presented a similar pattern of annual CBC risk after primary cancer. However, subgroup analyses according to receptor status revealed that in younger patients with HER2 overexpression, the CBC risk peaked at 4.6 years after primary surgery compared to older women (Fig. 3). Within the HR + HER2− subtype, while older age showed a similar hazard rate, younger age was associated with an increased CBC risk rate at 7.1 years after surgery. Within the triple-negative subtype, both groups presented increasing trends of CBC risk over time after surgery (Fig. 3).

Discussion

This study shows that younger women with breast cancer are at an increased risk of CBC compared to older women. Overall, the triple-negative subtype is associated with a high risk of CBC in both age groups. In the younger patients, HER2 overexpression, family history, and anti-hormone treatment were associated with higher CBC rates than in the older women. Following intrinsic subtype classification, the CBC risk pattern showed different timings of occurrence: in HER2-positive patients, CBC occurrence peaked within 5 years after surgery (peak 4.6 years), in HR-positive patients, the occurrence peaked more than 5 years after

Table 1 Patient characteristics according to age group

Characteristics	< 35 years ($n = 652$)	≥ 35 years ($n = 2608$)	*P*
Age at diagnosis, years (median ± SD)	32 ± 2.83	47 ± 9.43	
Follow-up time at diagnosis, months (median ± SD)	131 ± 41.58	128 ± 39.76	0.184
Family history[a]			
Yes	59 (9.0)	215 (8.3)	0.528
No	593 (91.0)	2391 (91.7)	
Unknown	0	2	
BMI (kg/m^2)			
< 18.5	72 (11.0)	79 (3.0)	< 0.01
≥ 18.5, < 25.0	484 (74.2)	1800 (69.0)	
≥ 25.0	96 (14.7)	729 (28.0)	
Pathologic T stage			
T1	293 (44.9)	1172 (44.9)	1.000
T2	305 (46.8)	1220 (46.8)	
T3	44 (6.7)	176 (6.7)	
T4	10 (1.5)	40 (1.5)	
Node metastasis			
No	348 (53.4)	1392 (53.4)	1.000
Yes	304 (46.6)	1216 (46.6)	
Histology			
Ductal	644 (98.8)	2538 (97.3)	0.016
Lobular	4 (0.6)	60 (2.3)	
Others	4 (0.6)	10 (0.4)	
Histologic grade			
1/2	591 (90.8)	2364 (90.8)	1.000
3	60 (9.2)	240 (9.2)	
IHC subtype			
HR-positive/HER2-negative	309 (47.4)	1236 (47.4)	1.000
HR-negative/HER2-positive	95 (14.6)	380 (14.6)	
HR-positive/HER2-positive	79 (12.1)	316 (12.1)	
HR-negative/HER2-negative	169 (25.9)	676 (25.9)	
Unknown			
Type of surgery			
Breast-conserving	391 (60.0)	1576 (60.4)	0.858
Mastectomy	261 (40.0)	1032 (39.6)	
Radiotherapy			
Yes	340 (52.1)	1427 (54.7)	0.202
No	311 (47.7)	1166 (44.7)	
Unknown	1	15	
Chemotherapy			
Yes	554 (85.0)	1907 (73.1)	< 0.01
No	97 (14.9)	681 (26.2)	
Unknown	1	20	
Hormone therapy			
Yes	381 (58.4)	1671 (64.1)	0.007
No	264 (40.5)	905 (34.7)	
Unknown	7	32	

Results are presented as no. of patients (%) unless otherwise noted. *P* values were assessed using a Chi-square test to compare the clinicopathologic characteristics with age. Cohort M is a matched cohort adjusted for tumor size, lymph node metastasis, subtype, and tumor grade

SD standard deviation, *BMI* body mass index, *IHC* immunohistochemical staining, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2

[a]Family history: First- and second-degree relative breast cancer family history

Table 2 Patient characteristics according to age at CBC diagnosis

	FBC			CBC		
	< 35 years ($n=43$)	≥ 35 years ($n=65$)	*P*	< 35 years ($n=43$)	≥ 35 years ($n=65$)	*P*
Time since first breast cancer, months [median ± SD (range)]				73 ± 49.7 (6–206)	73 ± 54.4 (7–230)	0.561
Pathologic T stage						
T0	0	0	0.357	4 (9.3)	10 (15.4)	0.71
T1	14 (32.6)	22 (33.8)		27 (62.8)	37 (56.9)	
T2	26 (60.5)	31 (47.7)		10 (23.3)	13 (20.0)	
T3	2 (4.7)	9 (13.8)		2 (4.7)	5 (7.7)	
T4	1 (2.3)	3 (4.6)		0	0	
Node metastasis						
No	22 (51.2)	37 (56.9)	0.693	36 (83.7)	47 (73.4)	0.392
Yes	21 (48.8)	28 (43.1)		7 (16.3)	17 (26.6)	
Unknown				0	1	
Histologic type						
Ductal	43 (100)	65 (100)		40 (93.0)	59 (92.2)	1.000
Lobular	0	0		0	1 (1.6)	
Others	0	0		3 (7.0)	4 (6.3)	
Unknown	0	0		0	1	
Histologic grade						
1/2	35 (81.4)	60 (92.3)	0.130	21 (50.0)	32 (52.5)	0.843
3	8 (18.6)	5 (7.7)		21 (50.0)	29 (47.5)	
Unknown				1	4	
Biomarker subtype						
HR-positive/HER2-negative	10 (23.3)	20 (30.8)	0.557	10 (24.4)	21 (39.6)	0.401
HR-positive/HER2-positive	7 (16.3)	7 (10.8)		4 (9.8)	6 (11.3)	
HR-negative/HER2-positive	5 (11.6)	4 (6.2)		5 (12.2)	6 (11.3)	
HR-negative/HER2-negative	21 (48.8)	34 (52.3)		22 (53.7)	20 (37.7)	
Unknown				2	12	
Type of surgery						
Breast-conserving	22 (52.4)	32 (50.8)	1.000	25 (61.0)	35 (54.7)	0.525
Mastectomy	20 (47.6)	31 (49.2)		16 (39.0)	29 (45.3)	
Unknown	1	2		2	1	

Results presented as no. of patients (%) unless otherwise noted. *P* values were assessed using a Chi-square test

SD standard deviation, *FBC* first breast cancer, *CBC* contralateral breast cancer, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2

surgery (peak 7.1 years), and in the triple-negative subtypes, the occurrence rate increased steadily over time.

In the present study, younger women whose first tumor showed HER2 overexpression had a higher risk of CBC than both women diagnosed after the age of 35 years (hazard ratio 4.98, 95% CI 2.19–11.33, eTable2) and younger women with HER2-negative tumors (hazard ratio 2.00, 95% CI 1.31–3.06, eTable2). Our results are in line with those of a previous study by Li et al., who reported that younger women whose first tumors overexpress c-erbB-2 have a greater risk of CBC. Women younger than 45 years whose initial tumor showed HER2 overexpression had a 1.7-fold (95% CI 1.0–3.0) higher CBC risk [15]. In contrast, some studies have failed to find an association between CBC and HER2-positivity [3, 22]. A large population-based cohort study conducted by the California Cancer Registry reported that the HER2 status of primary breast cancer was not associated with second primary breast cancer risk [3]. However, that study cohort included all age groups and hence did not identify the age-related relative CBC risks. Therefore, it remains unclear whether the risk of CBC is higher in younger HER2-positive women.

Killelea et al. [23] analyzed the National Cancer Database and demonstrated that younger women were significantly likelier to have HER2-positive breast cancer than older women. Furthermore, Kim et al. [21] showed that younger

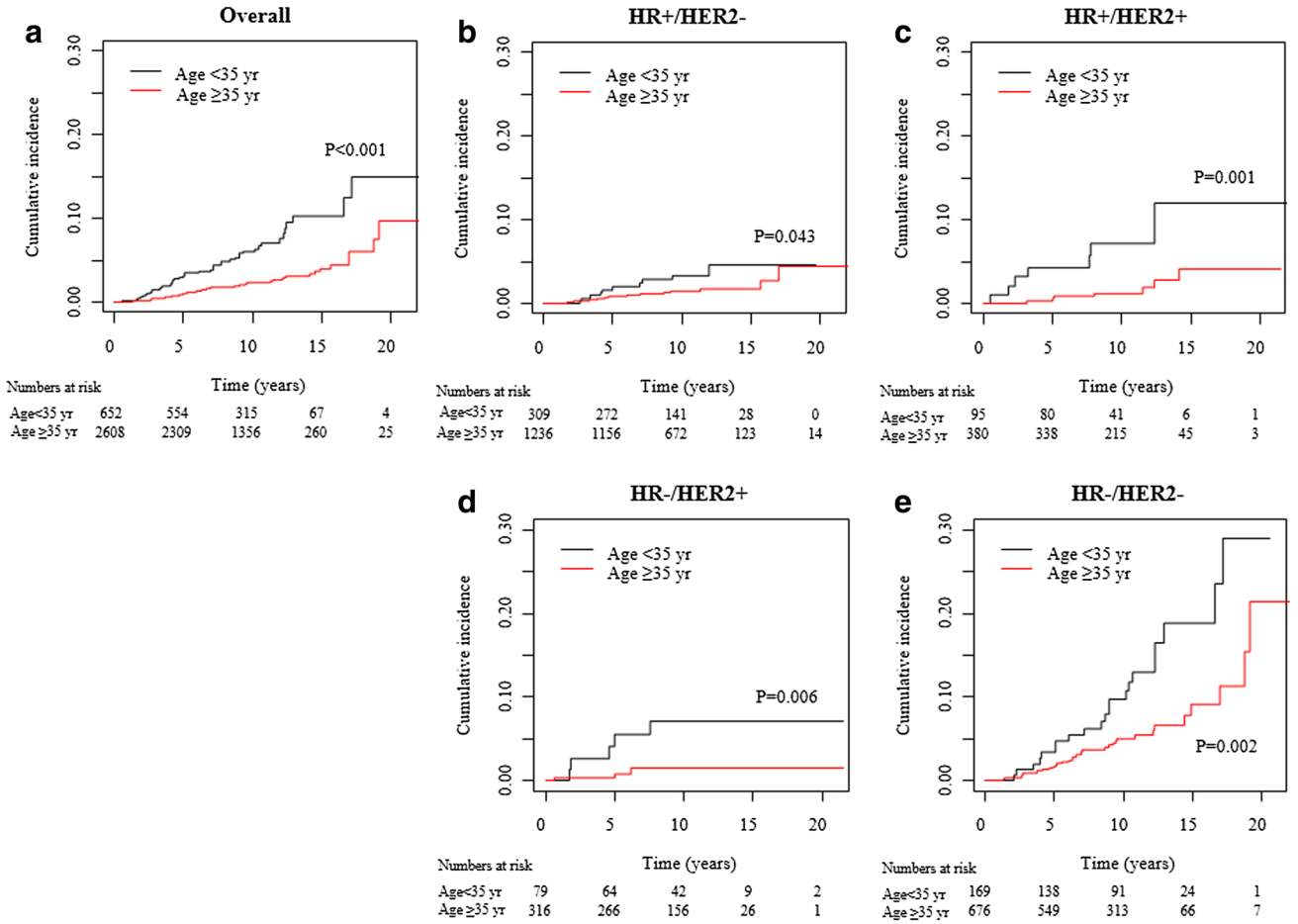

Fig. 1 Contralateral breast cancer-free survival according to age in all patients (**a**) and in subgroup analysis by subtype (**b**–**e**). *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2

breast cancer patients with the HER2-enriched subtype had a higher rate of ipsilateral breast tumor recurrence after breast-conserving surgery and radiotherapy than older patients. Our data showed that younger women with HER2-positive cancer were at a higher risk of CBC development. Additionally, annual risk analysis showed that this elevated risk appeared within 5 years after the primary tumor. Numerous studies have shown an association between younger onset age and HER2 overexpression [15, 21, 23], but the underlying mechanism remains unclear. Further investigation is required to confirm the relationship between young age and HER2 overexpression.

Our results revealed that breast cancer patients with the HR−/HER2− subtype showed a substantially higher cumulative risk of CBC (9.7% for younger and 5% for older patients at 10 years) than the other subtypes. Triple-negative breast cancer cannot benefit from hormone therapy and contributes to an increased risk of CBC in women with BRCA1 mutation-positive breast cancer [24]. Moreover, the BRCA mutation, especially BRCA1, increases the risk of CBC. Breast cancer-associated BRCA1 commonly presents a triple-negative subtype (commonly, a basal-like subtype), and a previous study in Korea reported an increase in the development of HER2-positive cancers among BRCA2 carriers [25]. Although the BRCA mutation was not investigated in our study, the high CBC rate observed in the triple-negative tumor cases could be associated with the BRCA mutation. The CBC risk associated with BRCA mutation increases with decreasing age at first diagnosis [4, 11, 26, 27]. Our results show that family history with younger age presented a greater risk of CBC than older age (hazard ratio 7.79; 95% CI 2.44–24.85). This finding suggests that younger patients with BRCA mutations may have a higher CBC rate. Congruently, a systematic review performed by Molina-Montes et al. [28] reported that, following the first breast cancer diagnosis, the cumulative risk of CBC increases over time in breast cancer patients with BRCA mutations. This is consistent with our findings which state that the triple-negative subtype is associated with a steady increase in the annual risk of CBC.

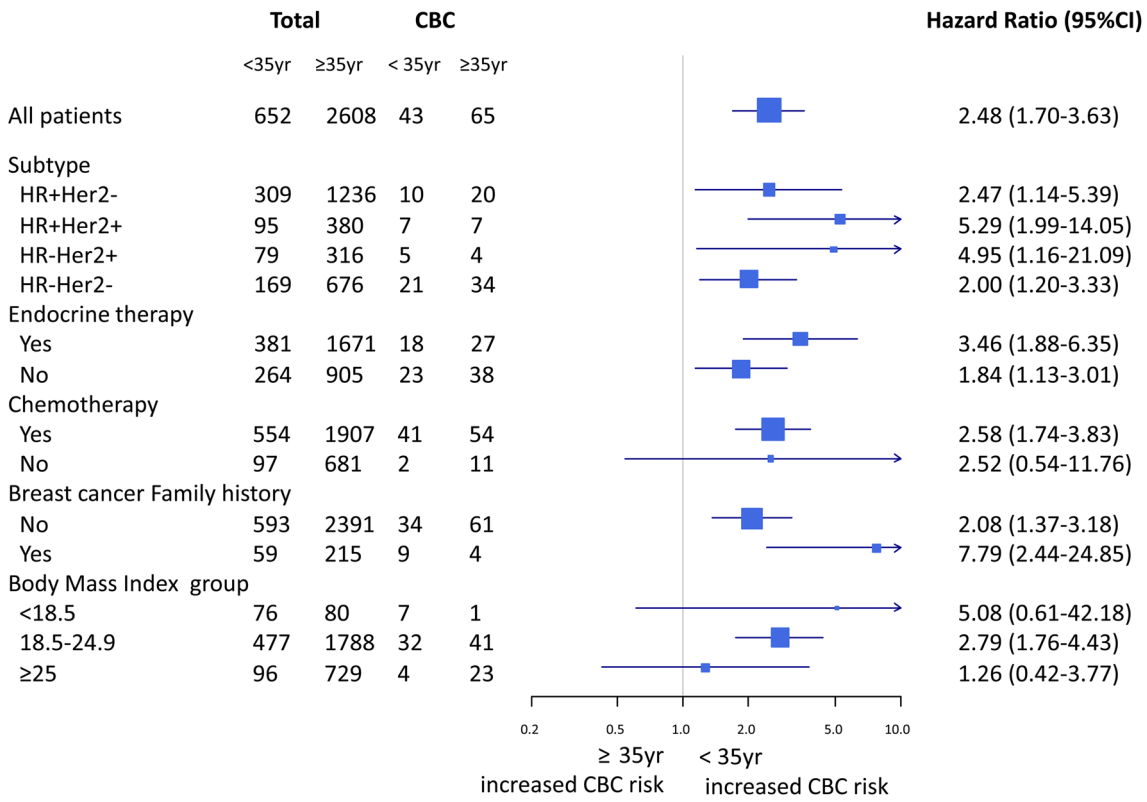

Fig. 2 Hazard ratio of contralateral breast cancer associated with age. Box size is based on precision, such as standard error of hazard ratio. *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2, *CBC* contralateral breast cancer, *CI* confidence interval

In this study, younger patients who received endocrine therapy had a higher rate of CBC than older patients with endocrine therapy. Endocrine therapy for primary breast cancer protects against CBC [4, 5, 29, 30]. In their 2017 study of 7,541 patients, Gierach et al. [5] reported that the CBC risk decreased significantly with an increasing duration of endocrine therapy, suggesting that breast cancer patients should be encouraged to receive endocrine therapy. We observed that for younger patients with HR+/HER2− tumors, the CBC risk peaked after 5 years. Although the specific regimen and duration of endocrine therapy regimen were not known in this retrospective study, the increase observed in the rate of HR-positive breast cancer after 5 years may be associated with the cessation of endocrine therapy. Davies et al. [31] showed that continuing adjuvant hormone therapy for up to 10 years improved survival. Although the *P* value did not reach significance ($P = 0.07$), taking tamoxifen for 10 years resulted in a lower CBC rate than taking it for 5 years (hazard ratio 0.88; 95% CI 0.77–1.01). Taken together, those results indicate that long-term hormone therapy in young women may contribute to CBC prevention.

The main limitation of the present study was the relatively small number of CBC events. Additionally, the study was limited by a lack of data on BRCA status. Breast cancer rarely presents in women younger than 35 years, and genetic test results and the risk for second primary cancer in the contralateral breast need to be analyzed in light of BRCA results, in addition to family history. Finally, since the Korea Health Insurance offered limited coverage for targeted therapy before 2008, the present study included only four patients receiving trastuzumab. A meta-analysis of randomized controlled trials in 2011 showed that targeted therapy did not exert a significant influence on the risk of CBC [24]. However, additional studies on patients who received targeted therapy tailored to the current guidelines need to be conducted.

Despite the limitations, our study gathered important information: we determined the CBC risk in young women and compared the relative risk factors between younger and older women, using a matched cohort adjusted for various factors that may influence CBC development.

To the best of our knowledge, our study is the first to compare the age-related risk factors for CBC via propensity score matching to minimize potential bias. Few large-scale studies focusing on younger age groups have addressed the tumor subtype. In addition, our study confirmed the annual hazard risk, analyzed the difference in the time of occurrence, and had a relatively long follow-up period for CBC.

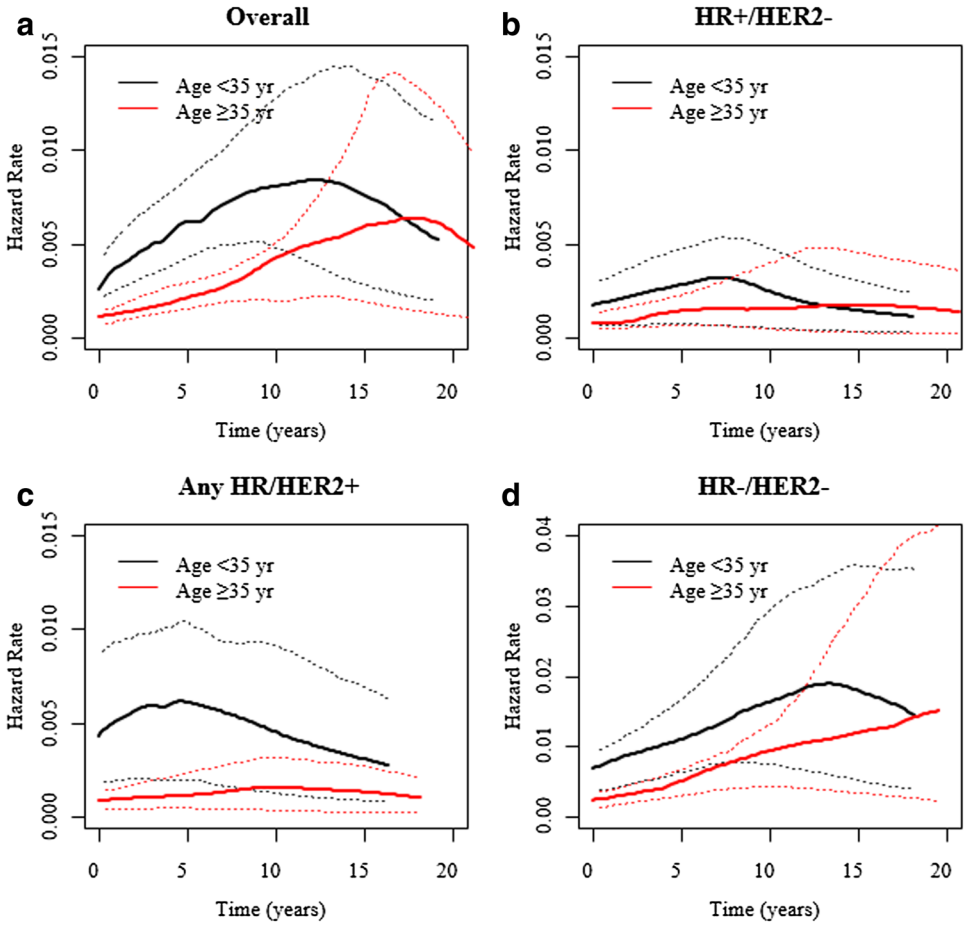

Fig. 3 Smoothed annual risk of contralateral breast cancer after primary surgery. *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2

Conclusion

After adjusting for primary breast tumor characteristics, women aged under 35 years had 2.5 times the risk of CBC development compared to the older women, especially those with the HER2-positive subtype or a family history of breast cancer. The risk in the younger group was even higher among those without a family history of the disease. Antihormone treatment was associated with reduced CBC rates during treatment, but its efficiency in young breast cancer patients is poorer than that in older patients. CBC in the younger women presented earlier than in the older women, occurring within 5 years in those with the HER2-positive subtype but after 5 years in those with the HR-positive subtype after primary breast cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have conflict of interest

Research involving human participants and/or animals This article does not contain any studies with human participants performed by any of the authors.

Informed consent Not applicable.

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