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Original contribution

Synchronous and metachronous bilateral breast cancer: clinicopathologic characteristics and prognostic outcomes☆

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Summary The incidence of bilateral breast cancer (BBC) reportedly ranges from 1.4 to 11.8%. Women with a first primary breast cancer are at a 2- to 6-fold increased risk of developing contralateral BC. However, there have been limited studies analyzing the clinicopathologic features of BBC and conflicting data exist on the prognostic significance of BBC. In this study, we sought to analyze the incidence of BBC in the era of modern medicine and assess the clinicopathologic characteristics and prognostic outcomes compared to unilateral BC (UBC). Of the 5941 patients with stage I-III BC diagnosed between 1998 and 2013 at our institution, 110 developed BBC, including 58 synchronous BBC (SBBC, interval between the first and the contralateral BC ≤3 months) and 52 metachronous BBC (MBBC, interval >3 months). The median time to the second tumor was 67.9 months among patients with MBBC. BBC was associated with a significantly lower rate of having a ductal type, high grade, HER2-positive or node-positive disease when compared to UBC, while no difference was found for age, race, ER/PR status, or pathologic tumor stage. When compared to MBBC, SBBC was strongly associated with a lobular phenotype, non-high grade, and ER/PR-positive disease; and further demonstrated a significantly higher concordant rate for ER, PR, and HER2 status. Patients with BBC had a significantly worse distant relapse-free survival (RFS) but a similar disease-specific survival (DSS) when compared to those with UBC. Being African American, having a high histologic grade and higher pathologic tumor or node stage was significantly associated with a worse prognosis, while SBBC was associated with a favorable RFS by multivariate analysis. Nodal status was the only independent prognosticator for DSS in patients with BBC. Further investigation into the complex biologic and clinical behavior of BBC may provide novel insights into the therapeutic strategies in the pursuit of precision medicine in this unique subset of patients.

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1. Introduction

Breast cancer is the most common cancer and the second leading cause of cancer death in American women, with an estimated 268 600 new cases and 41 760 deaths in 2019, respectively [1]. The most common second malignancy in patients with breast cancer is carcinoma of the contralateral breast [2]. The risk for women with unilateral breast cancer (UBC) of developing a contralateral breast cancer is 2- to 6-fold the risk in the general population of women developing a first primary cancer. The incidence of bilateral breast cancer (BBC) reportedly ranges from 1.4% to 11.8% in women diagnosed with breast cancer [3].

Although reported criteria vary, BBC is generally separated into synchronous (SBBC) and metachronous (MBBC) variants when a contralateral breast cancer is diagnosed within or more than 3 months after diagnosis of the first tumor, respectively [4]. There are scarce epidemiological studies for risk factors for BBC. A family history of breast cancer, a young age at initial diagnosis or a germ-line mutation in the *BRAC1* or *BRCA2* genes are associated with an increased risk of developing a contralateral tumor, identifying these women as generally high risk individuals [3]. A number of early studies have found a strong correlation with a lobular histology in the first primary breast cancer and the occurrence of BBC [5-8].

Table 1 Clinicopathologic characteristics of unilateral and bilateral breast cancer

Clinicopathologic factor	UBC (n = 5832)	BBC (n = 110)	SBBC (n = 58)	MBBC (n = 52)	*P* (UBC *vs* BBC)	*P* (SBBC *vs* MBBC)
Age (mean/median/range)	56/56/29-88	59/59/29-88	58/59/33-85	56/57/29-88		
≤50 years	2062	33	14	19	.33	.26
>50 years	3770	77	44	33		
Race						
Caucasian	4452	93	50	43	.10	.80
African American	1296	17	8	9		
Others	84					
Histologic type [a]						
Ductal	5100	165	80	85	<.0001	.04
Lobular	709	55	36	19		
Other	23					
Histologic grade [a]						
Grade I	906	41	28	13	.0004	.0004
Grade II	2219	117	68	49		
Grade III	2196	62	20	42		
Unknown	511					
Estrogen receptor [a]						
Positive	3728	165	97	68	.51	.003
Negative	1397	55	19	36		
Unknown	707					
Progesterone receptor [a]						
Positive	3169	141	85	56	.65	.004
Negative	1917	79	31	48		
Unknown	746					
HER2 [a]						
Positive	716	26	10	16	.02	.2
Negative	2965	178	99	79		
Unknown	2151	16	7	9		
Pathologic stage [a]						
pT1	2810	134	71	63	.72	.52
pT2	1562	69	34	35		
pT3/pT4	430	17	11	6		
Unknown	1029					
Lymph node status [a]						
pN0	2893	155	83	72	.01	.92
pN1-3	1669	60	31	29		
pNX	1270	5	2	3		

Abbreviations: UBC, unilateral breast cancer; BBC, bilateral breast cancer; SBBC, synchronous bilateral breast cancer; MBBC, metachronous bilateral breast cancer.

[a] The pathologic factors include bilateral breast cancers.

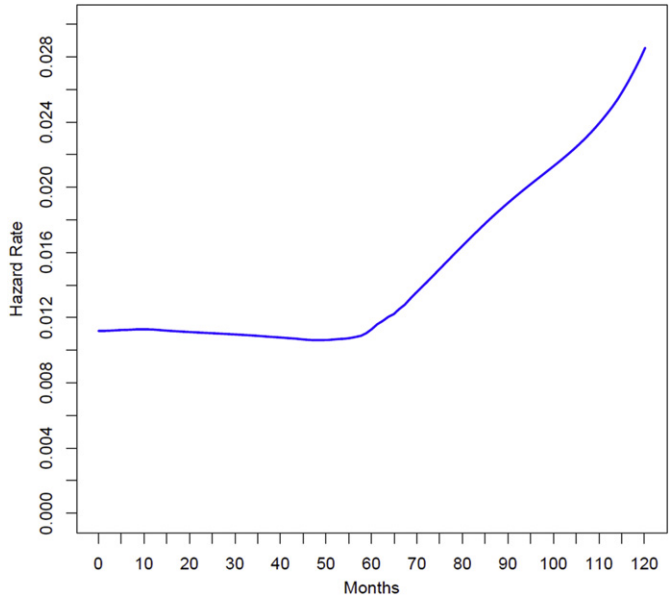

Fig. 1 Smoothened hazard rates for developing a contralateral breast cancer in patients with metachronous bilateral breast cancer.

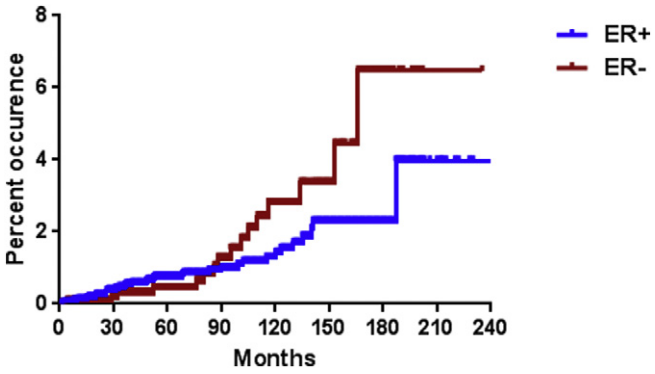

Fig. 2 Cumulative incidence graphs for developing a contralateral breast cancer in patients with metachronous bilateral breast cancer stratified by ER status of the first tumor.

Table 2 Pathologic similarity between bilateral breast cancers

Pathologic factor	SBBC	MBBC	*P*
Histologic type			
Concordant	48	39	.45
Discordant	10	13	
Histologic grade			
Concordant	35	26	.37
Discordant	23	26	
Estrogen receptor			
Concordant	49	30	.004
Discordant	9	22	
Progesterone receptor			
Concordant	47	30	.001
Discordant	11	22	
HER2			
Concordant	51	32	.01
Discordant	3	11	

Abbreviations: SBBC, synchronous bilateral breast cancer; MBBC, metachronous bilateral breast cancer.

This observation was in the era when mirror image biopsy was advocated for lobular carcinomas thus this could arguably have increased detection of contralateral breast cancers; however, more recent studies have also shown a similar trend [9,10].

There have been only limited studies analyzing the clinical and pathologic features of BBC, and the results on incidence rates and temporal trends are controversial. Moreover, conflicting data exist on the prognostic significance of BBC, be they synchronous or metachronous. In this study, we sought to compare the clinicopathologic characteristics between BBC and UBC in a large cohort of breast cancer patients. We also analyzed the impact of SBBC and MBBC on survival outcomes in patients with BBC.

2. Materials and methods

After approval by the Institutional Review Board of the University of Alabama at Birmingham, the UAB Tumor Registry was searched to identify patients diagnosed with invasive breast cancer between 1998 and 2013. The patients' demographic information including age at initial diagnosis and race, and the pathologic features of the tumor, including histologic grade, estrogen/progesterone receptor (ER/PR) and human epidermal growth factor receptor 2 (HER2) status, tumor size and lymph

node status along with the follow-up data were recorded. The data was further verified using the electronic medical record and/or surgical pathology database. Patients with stage IV disease at initial diagnosis, those with distant relapse before the diagnosis of contralateral breast cancer, and those who did not receive standard of care treatment at the time of diagnosis were not included. Breast cancer was categorized as UBC or BBC while the latter was further divided into SBBC or MBBC based on the interval between the first and the contralateral tumors (≤3 and >3 months, respectively) [11]. The median follow up time were 5.7 and 10 years for the patients with UBC and BBC, respectively.

A 10% cutoff was used for ER and PR interpretation in the early years whereas this cutoff was changed to 1% following the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline recommendations in 2010 [12]. HER2 overexpression/gene amplification was defined as either a 3+ immunohistochemistry score (uniform and intense membrane staining of >30% of tumor cells) or as a positive in situ hybridization result following the ASCO/CAP guideline recommendations [13]. Breast cancer subtypes were classified by a combination of hormonal receptors and HER2 status, including luminal (ER+ and/or PR+; HER2−), luminal/HER2 (ER+ and/or PR+; HER2+), HER2 (ER−/PR−/HER2+), or triple-negative breast cancer (TNBC; ER−/PR−/HER2−).

The categorical data obtained were statistically evaluated using the Chi-square test, while continuous data were evaluated using the Student *t* test. The distant relapse-free survival (RFS) was defined as the time from the initial diagnosis to the date of first distant metastasis or to the follow-up cutoff. The disease-specific survival (DSS) was defined as the length of time from the initial diagnosis to the date of death from the disease or study cutoff. Patients who survived or were lost to follow-up were considered as censored data in the analysis. Kaplan-Meier curves were used to estimate survival. The Log-Rank test was used to compare differences between groups. The χ^2 statistic of the Log-Rank test was used calculate the discrimination between groups. The cumulative incidence of BBC from the time of initial diagnosis was calculated similarly. The Cox proportional hazards regression model was utilized to determine the association between clinicopathologic factures and survival outcomes. A *P*-value of less than .05 was considered statistically significant. Statistical analysis was performed by utilizing SAS v9.1 software (SAS Institute Inc, Cary, NC).

3. Results

3.1. Clinicopathologic characteristics and hazard estimates

Of the 5941 patients meeting the inclusion criteria in the study period, 110 (1.9%) were diagnosed with BBC, including 58 SBBC and 52 MBBC, respectively. The clinicopathologic characteristics of BBC are summarized in Table 1. The median time to the second tumor was 67.9 months (range, 3.1-216.5) among patients with MBBC. A smoothened hazard rates for the occurrence of the second tumor in the patients with MBBC are shown Fig. 1, in which a stable hazard rate of about 60 months followed by a constant increase had been observed. Since the benefit of endocrine therapy reportedly lasts for up to 5 years after first diagnosis, we next assessed the cumulative

Table 3 Subtypes of bilateral breast cancer

SBBC (58)		MBBC (52)	
First primary	Second primary	First primary	Second primary
Luminal (41)	Luminal (37) Luminal/HER2 (2) TNBC (2)	Luminal (28)	Luminal (18) Luminal/HER2 (2) TBNC (7) HR+/HER2 unk (1)
Luminal/HER2 (4)	Luminal (1) Luminal/HER2 (3)	Luminal/HER2 (8)	Luminal (4) HER2 (1) TNBC (3)
HER2 (1)	HR-/HER2 unk (1)	HER2 (2)	HER2 (1) TNBC (1)
TNBC (9)	Luminal (6) TNBC (3)	TNBC (7)	Luminal (3) Luminal/HER2 (1) TNBC (2) HR+/HER2 unk (1)
HR+/HER2 unk (2)	HR+/HER2 unk (2)	HR+/HER2 unk (3)	Luminal (2) TNBC (1)
HR-/HER2 unk (1)	HR-/HER2 unk (1)	HR-/HER2 unk (4)	Luminal (2) Luminal/HER2 (1) TBNC (1)

Abbreviations: SBBC, synchronous bilateral breast cancer; MBBC, metachronous bilateral breast cancer; TNBC, triple-negative breast cancer; unk, unknown; HR, hormonal receptor.

incidence of the occurrence of the second tumor based on the ER status of the first primary breast cancer. Interestingly, the incidence proportions of the ER+ and ER- categories largely overlapped for approximately 84 months (7 years) before they diverged (Fig. 2).

When compared to UBC, BBC was associated with a significantly lower rate of ductal (no special) type, high histologic grade, HER2-positivity, and node-positive disease, while no difference was found for age, race, ER and PR status, or pathologic tumor stage.

When analyzing the group of patients with BBC, SBBC was strongly associated with a lobular phenotype, non-high histologic grade, and ER-positive and PR-positive disease when compared to MBBC, whereas age, race, HER2, pathologic tumor stage and nodal status showed no statistical difference between the two groups.

In an attempt to compare the histopathologic similarities of BBC, SBBC was found to be significantly associated with a higher concordant rate for ER, PR, and HER2 status when compared to MBBC while no difference was found for histologic type or grade (Table 2). Given that breast cancer subtypes have prognostic significance including response to systemic therapy and survival outcomes, we next compared the subtype similarities of BBC. As illustrated in Table 3, SBBC was significantly associated with a higher concordant rate for the subtypes when compared to MBBC (43/54, 80% versus 21/43, 49%; $P = .001$). Analysis of MBBC cases revealed that 31% (12/39) of patients with hormonal receptor positive (HR+) first primary breast cancer developed a second HR- (HER2 subtype or TNBC) primary tumor, whereas 38% (8/13) of patients with HR- first primary breast cancer developed a second HR- primary tumor ($P = .74$). On the other hand, only 20% (2/10) of patients with a first HER2+ tumor developed a subsequent HER2+ cancer.

3.2. Prognostic outcomes

In the analyses to compare the prognostic outcomes of UBC and BBC, patients with BBC were found to have a significantly worse RFS [HR 1.883 (1.273, 4.184), $P = .007$] when compared to those with UBC. However, no significant difference was found for DSS [HR 0.8561 (0.4838, 1.547), $P = .63$] (Fig. 3).

We next turned to establish the significant prognostic factors in this cohort of patients with BBC. To that end, individuals self-identifying as African American, having a high histologic grade and higher pathologic tumor or node stage were significantly associated with a worse RFS and DSS among patients with BBC by univariate analysis. No significant difference was found between SBBC and MBBC (Table 4; Fig. 4). In multivariate Cox regression

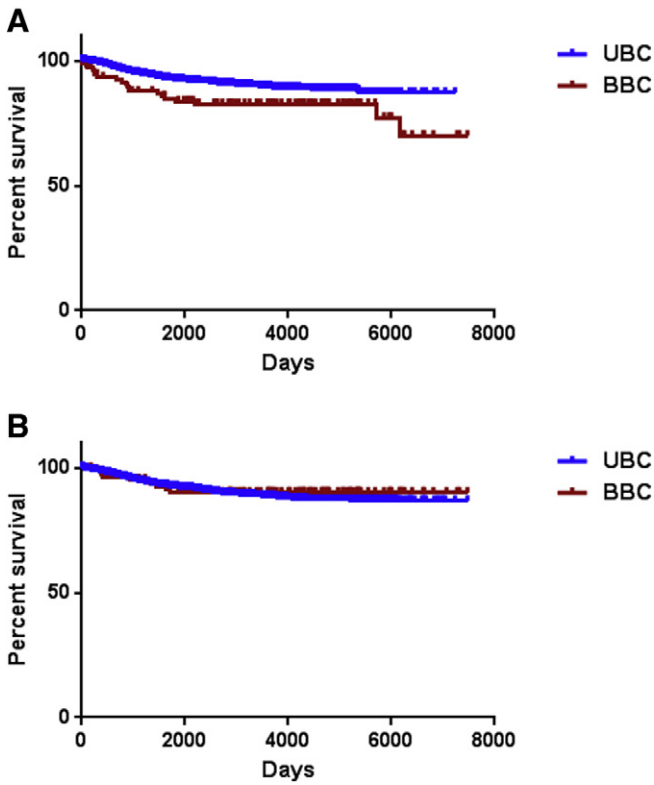

Fig. 3 Distant relapse-free survival (A) and disease specific survival (B). UBC, unilateral breast cancer; BBC, bilateral breast cancer.

Table 4 Univariate analysis for relapse-free and disease-specific survivals in patients with bilateral breast cancer

Clinicopathologic factors	Relapse-free survival		Disease-specific survival	
	HR [95% CI]	*P*	HR [95% CI]	*P*
Age	0.991 [0.957, 1.027]	.62	0.996 [0.948, 1.046]	.86
Race (White *vs* AA)	0.2416 [0.03082, 0.3891]	.0007	0.2790 [0.02881, 0.8711]	.03
Tumor type (ductal *vs* lobular)	1.194 [0.4189, 3.364]	.75	1.363 [0.3207, 5.529]	.69
Histologic grade (I/II *vs* III)	0.4107 [0.1362, 0.9380]	.04	0.1423 [0.03417, 0.3245]	<.0001
ER (positive *vs* negative)	0.5068 [0.1771, 1.215]	.12	0.2586 [0.05101, 0.8079]	.02
PR (positive *vs* negative)	0.5770 [0.2334, 1.384]	.21	0.4546 [0.1260, 1.574]	.21
HER2 (positive *vs* negative)	1.765 [0.4448, 9.449]	.36	1.038 [0.1260, 8.562]	.97
Pathologic stage (pT)	3.016 [1.947, 4.672]	7.6×10^{-7}	3.407 [1.911, 6.074]	3.26×10^{-5}
Lymph node status (negative *vs* positive)	0.1308 [0.03560, 0.2499]	<.0001	0.04378 [0.01185, 0.1859]	<.0001
SBBC *vs* MBBC	0.7632 [0.3105, 1.821]	.54	1.242 [0.3567, 4.304]	.74

Abbreviations: HR, hazard ratio; CI, confidence interval; AA, African American.

analyses, race [HR 0.2675; 95% CI (0.09557, 0.7487); *P* = .01], pathologic tumor stage [HR 2.7514; 95% CI (1.4699, 5.1505); *P* = .002] and node stage [HR 7.2946; 95% CI (2.0150, 26.4074); *P* = .002] remained significant for RFS. Interestingly, after adjusted for potentially confounding variables, SBBC was an independent predictor of a favorable RFS [HR 0.2540; 95% CI (0.0703, 0.9179); *P* = .04]. Notably, the nodal status was the only significant prognosticator for DSS in multivariate analysis [HR 6.0443; 95% CI (1.0174, 35.9071); *P* = .048]. It should further be noted that while the survival analyses utilized the pathologic characteristics of the contralateral (second) breast cancers, similar results were obtained when applying those of the first primaries by both univariate and multivariate analyses (data not shown).

The hazard rates for distant relapse and DSS according to UBC, SBBC and MBBC were estimated. SBBC and MBBC had largely overlapped hazard rates of distant relapse, but demonstrated a higher hazard rate as a group of BBC, when compared to UBC. All three groups

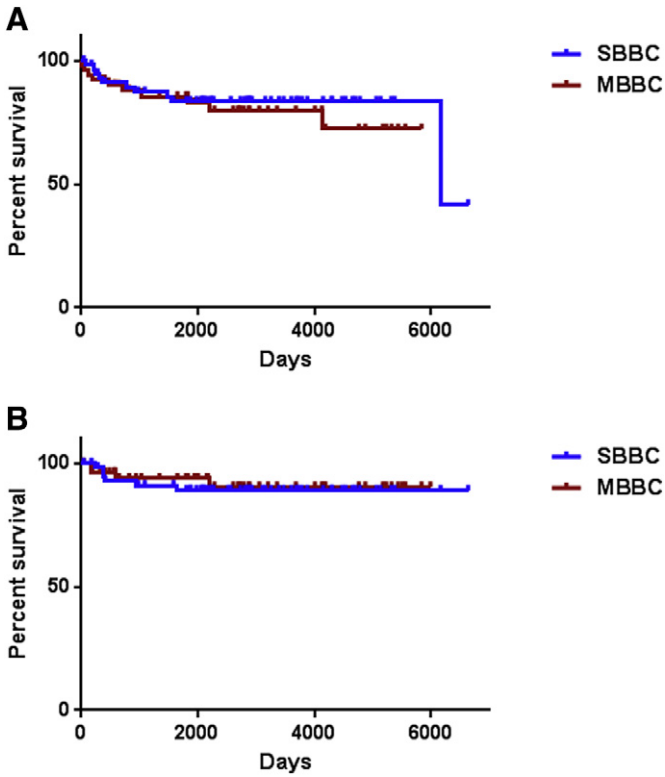

Fig. 4 Distant relapse-free survival (A) and disease specific survival (B). SBBC, synchronous bilateral breast cancer; MBBC, metachronous bilateral breast cancer.

exhibited similar, comparable trends for DSS. These findings largely reflect the aforementioned prognostic outcomes.

4. Discussion

Contralateral breast cancer as a second primary tumor was first described in 1921, in which a higher risk of developing second primary contralateral breast cancer was found in women diagnosed with breast cancers than the risk of developing a first primary breast cancer in the general population [14]. This important public health issue has been increasingly recognized ever since due to the growing breast cancer incidence and improved survival of breast cancer patients.

The incidence of BBC, however, is considerably lower in most recent studies, including ours. This is most likely due to the aggressive screening and advancements in systemic therapy in the last two decades. The prevalence of SBBC was reported as high as 4% when MRI screening was employed in a meta-analysis [15]. The risk for contralateral second primary breast cancers reportedly varies substantially by hormonal receptor status of the first tumor, and age, and race and/or ethnicity [16]. An early large cohort study of Swedish women from 1970 to 2000 found an increase in the incidence of SBBC, likely due to the introduction of mammography, whereas a decreased incidence of MBBC was observed, probably owing to the introduction of systemic adjuvant therapy [4].

A notable interesting observation in this study was that a stable hazard rate for about 60 months followed by a constant increase was observed in the group of patients with MBBC. This is in contrast to a study of 4065 women with breast cancer diagnosed from 1983 to 2011, in which a constant increase was observed with a peak at about 254 months followed by a decline [17]. It has been reported that adjuvant systemic hormonal therapy for ER+ disease reduces the incidence of contralateral breast cancer by 39% to 55%, depending on menopausal status [18]. Moreover, this benefit seems to last for up to 5 years after first diagnosis and is largely due irrespective of the use of chemotherapy and of age, PR or other tumor characteristics. These findings support our observations on the cumulative incidence of a second tumor in those patients with an ER+ first primary. Surprisingly, we also found that the incidence proportion of ER- first tumors largely overlapped with the ER+ primaries for up to 7 years and then diverged. One potential mechanism is the paradoxical clinical effect of estrogen on breast cancer risk that has been recognized in the last decade. Long-term antiestrogen therapy or estrogen deprivation causes the eventual development and evolution of antihormone resistance, an observation supported by laboratory models in which cancer cells emerge with a vulnerability, as estrogen is no longer a survival signal but is an apoptotic trigger [19]. Furthermore, chemotherapy is also associated with a lower risk for contralateral breast cancer and the reduced risk may persist up to 10 years after the first breast cancer diagnosis [20]. Thus, these findings provide plausible explanations for our observations. On the other hand, only 20% of patients with a first HER2+ tumor developed a subsequent HER2+ cancer in this cohort, possibly due to the effect of HER2-targeted therapy. Nonetheless, the median time to the second tumor was 67.9 months among patients with MBBC in this cohort study, in line with the those reported in previous studies which ranged from 3.9 to 7.7 years [11].

Two recent studies reported on increased risk of BBC for ER+ and PR+ tumors in patients of all races [16,21]. A similar trend was also obtained in this cohort, although this did not reach a significant statistical difference. Conversely, no increased incidence was found in German women [22], and a decreased risk was observed in the analyses from the California Cancer Registry [23] and the Geneva Cancer Registry [24]. Once again, this trend difference is most likely due to the use of more aggressive neoadjuvant chemotherapy when the first ER- breast cancers were diagnosed, and an increased number of prophylactic mastectomies of the contralateral breasts were performed. Moreover, patients carrying germ-line mutations in the *BRCA1* or *BRCA2* genes have an increased risk of developing BBC and the tumors in patients with *BRCA1* mutations are more commonly triple-negative. As the prevalence of *BRCA1* and *BRCA2* mutations is very low, and the trend for prophylactic bilateral mastectomy in healthy women and prophylactic contralateral mastectomy in women with UBC is steadily rising, most BBC patients do not carry these mutations, as indicated in an early study [25].

Our findings in the comparison of pathologic similarities between the two tumors, especially SBBC, are largely compatible with a previous epidemiologic study in which the ER status of BBC was highly concordant between the two tumors, while similar but weak trends were observed for PR status, tumor type and histologic grade when SBBC and MBBC were analyzed together [26]. In this regard, it is not surprising to observe a strong concordance in HER2 status in SBBC as the majority of the first primary tumors were HER2-. On the other hand, most of SBBC patients (3 out of 4) with a luminal/HER2 first primary tumor developed the same subtype of contralateral breast cancer, an interesting finding but one requiring further investigation given the small number of patients. Nonetheless, the phenotypic similarities of SBBC suggest predetermined biologic characteristics in the early stage of carcinogenesis of the two cancers that develop in a common tumor microenvironment with the same genetic makeup.

There has been conflicting data in the literature also whether developing a contralateral breast cancer influences prognostic outcomes. Bilaterality of breast cancer was found to be significantly associated with a worse overall or disease-specific survival when compared to

UBC in a number of studies [4,10,27,28]. Conversely, overall survival did not significantly differ for patients with BBC from those with UBC in other multivariate analyses [29-33], thus in harmony with the findings from this cohort study. Similarly, controversies also exist when comparing overall survival of patients with SBBC and those with UBC [9,17]. In agreement with an early observation [33], a significantly increased risk of distant metastasis was associated with BBC in the current study. In multivariate analysis among the patients with BBC, SBBC was found to be an independent favorable prognostic factor for RFS, but not DSS, when compared to MBBC in this cohort. On the contrary, SBBC was significantly associated with an increased hazard of distant metastasis and DSS in an aforementioned study including patients diagnosed between 1983 and 2011 [17].

There are some inherent limitations to this and all similar studies. First, one might argue that it is difficult to distinguish second primary contralateral breast cancers from metastases of the first primaries. However, BBC in this cohort was significantly associated with non-high grade disease, the patients demonstrated a lack of distant relapse before contralateral breast cancers, and more importantly, no significant difference for DSS was found between the patients with BBC and UBC. These observations all support the classification of these cases as primary contralateral breast cancers. Moreover, comparison of genetic alterations in paired tumors has demonstrated that bilateral breast malignancies most frequently represent two primary breast cancers, even though contralateral breast cancer spread does occur [34], further supporting our conclusion. Second, assessment of survival outcomes is difficult in BBC as the prognosis may be attributed to the first and/or second cancers. To that end, all survival analyses were carried out by using the pathologic characteristics of the first and second (contralateral) breast cancers, which yielded similar observations.

An important caveat is to compare our findings to similar studies and identify significant methodologic differences. The cutoffs used to distinguish SBBC from MBBC ranged from 1 to 12 months in the literature. A recent meta-analysis found that the HR of overall survival also depended on the interval time used. The HR and 95% CI of SBBC versus MBBC were 0.64 (0.44-0.94), 1.17 (0.84-1.63) and 1.45 (1.10-1.92) when using 3, 6 or 12 months as the cutoff time, respectively [28]. Most of the previous studies included patients diagnosed in the 1960's to 1980's [4,17,27,29-33], and some included patients diagnosed in the early 1990's [21]. Immunohistochemistry replaced the dextran-coated charcoal assay for hormonal receptor studies in the mid 1990's, and was first approved by ASCO/CAP for routine clinical practice in 1999 [35]. The guidelines also changed the historical cutoff values for ER/PR positivity from 10% to 1% [12]. Furthermore, wide implementation of the ASCO/CAP guidelines for HER2 testing was not available until 2007 [13]. More importantly, treatment strategies have changed significantly over the last few decades. Lastly, while there have been multiple large-scaled previous investigations providing good estimates of incidence and prognosis, most of them were meta-analyses of published studies given the rarity of BBC and thus could not provide more detailed clinical and pathologic characteristics when compared to those using a single-institution cohort. Thus, it is difficult to draw meaningful conclusions solely by comparison with these studies.

In summary, significant differences in some pathologic characteristics between BBC and UBC were identified in this study. BBC was associated with a shorter RFS, but a similar DSS when compared to UBC. Moreover, SBBC was associated with a favorable RSF but similar DSS when compared to MBBC when adjusted for other clinicopathologic factors in patients with BBC. While these findings require validation by large-scaled studies with prolonged follow-up, further investigation into the complex behavior of BBC may provide novel insights into the biological attributes and therapeutic strategies in the pursuit of precision medicine.

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