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EPIDEMIOLOGY

National trends of synchronous bilateral breast cancer incidence in the United States

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Abstract

Purpose Increase in breast cancer survivorship, advancements in diagnostic imaging and standardization of contralateral breast screening before breast cancer surgery have resulted in increased detection of contralateral breast cancer (CBC). The aim of this study was to assess national trends of synchronous bilateral breast cancer (sBBC) and metachronous bilateral breast cancer (mBBC) incidence in newly diagnosed breast cancer patients.

Methods The Surveillance, Epidemiology, and End Results (SEER) database (1973–2014) was used to identify 11,177 women diagnosed with CBC. CBC was classified as sBBC when primary breast cancer in both breasts is diagnosed in the same year, or as mBBC, when diagnosed more than one year from primary breast cancer. Temporal trends in sBBC incidence were then evaluated using the Cochran-Armitage test for trend.

Results Of the 11,177 women diagnosed with CBC, 4228 (38%) had sBBC and 6949 (62%) had mBBC. The incidence of sBBC increased significantly from 1.4% in 1975 to 2.9% in 2014 ($p < 0.001$). sBBC was more likely to be diagnosed as early stage in recent years (78% in 1975 vs. 90% in 2014 [$p < 0.001$]), and 69% of patients were treated with mastectomy in 2014.

Conclusion The number of sBBC has increased, and contralateral tumors are more likely to be detected at an early stage with the first primary breast cancer. Despite the early stage findings, most were treated with mastectomy. Further studies are needed to define the best therapy for patients with contralateral disease and optimal surveillance and detection methods.

Keywords Synchronous · Metachronous · Bilateral breast cancer · Incidence · Trends · SEER

Background

In recent years, more women are living with a breast cancer diagnosis due to increased breast cancer incidence, reduced breast cancer mortality, and improved life expectancy [1]. However, this increase in breast cancer survivorship also means that more women are at risk for developing contralateral breast cancer (CBC). CBC is classified as either synchronous BBC (sBBC), when CBC is diagnosed simultaneously with the first breast cancer, or metachronous BBC (mBBC), when CBC is diagnosed during long-term follow-up after the first breast cancer. Advancements in breast diagnostic imaging and routine use of contralateral breast screening result in increased detection of sBBC; however, there is limited data on the incidence and trends of sBBC or mBBC due to lack of widely accepted or standard definitions [2]. The aim of this study was to examine national trends in sBBC and mBBC incidence for newly diagnosed breast

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cancer patients in the United States using a large national database.

Materials and methods

The *Surveillance, Epidemiology, and End Results* (SEER) database of the National Cancer Institute provides information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries, which covers approximately 28% of the United States population. Because this study did not meet the definition of human subject research, the protocol was considered exempt from review from the Dana-Farber Cancer Institute Institutional Review Board. Inclusion criteria included female patients aged 20 years or older who were diagnosed with breast cancer between 1973 and 2014 and had surgery. The breast cancer cases and population data were obtained from the SEER 18 Registries Database (SEER 18, November 2016 submission). Since there is no special code in SEER to identify CBC patients, we extracted patients with at least one prior breast cancer and removed ipsilateral breast cancer records, according to laterality, cancer sequence number and multiple primary and histology coding rules in SEER. To evaluate trends in sBBC incidence, we chose patients whose CBCs were diagnosed at every 10 years (1975, 1985, 1995, 2005, and 2014). Although SEER data do not provide the exact date of breast cancer diagnosis, we defined sBBC as breast cancer in both breasts diagnosed in the same year, and defined mBBC as CBC diagnosed at more than 1 year after the first breast cancer. For each case of sBBC in our study, the breast containing the larger tumor was defined as the primary tumor and the contralateral smaller tumor was defined as contralateral tumor of sBBC. We included invasive and in situ cases as breast cancers in our study cohort, according to the TNM classification of AJCC 7th edition [3] which had been used until 2017. Histology and stages were coded in the database according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3); while stage at diagnosis is coded as in situ, local (localized to the breast), regional (spread to tissues surrounding the breast or to regional lymph nodes), distant (metastatic), or unknown. The crude incidence rates of bilateral breast cancer (BBC) were calculated by dividing the number of BBC patients by the number of newly diagnosed breast cancer cases in the same period. Among 190,871 breast cancer patients diagnosed in these years, we identified 16,567s breast cancers with at least one prior breast cancer record. We excluded 4803 patients with ipsilateral breast tumors and 587 patients who did not undergo breast surgery, resulting in 11,177 CBC patients for analysis (Fig. 1).

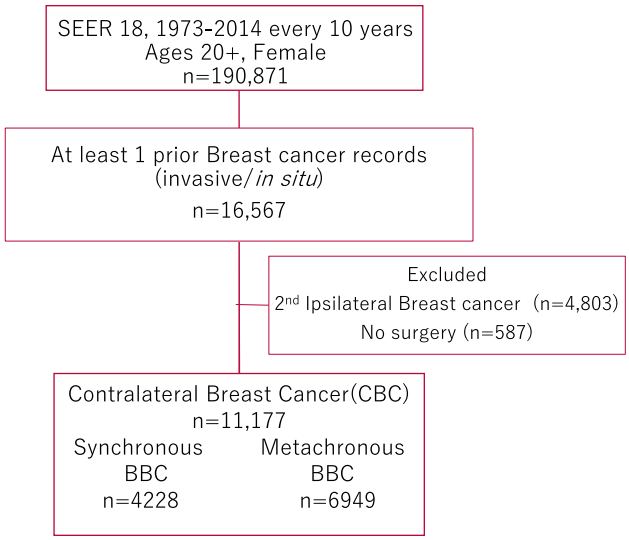


Fig. 1 Consort diagram

Baseline characteristics were compared using the Chi-squared test for categorical variables and Student's *T* test for continuous variables. To determine temporal trends of the incidence of sBBC, we used the Cochran-Armitage test for trends. All *p* values were two-sided, with a threshold of 0.05 used to indicate statistical significance. Statistical analyses were performed using JMP (SAS Institute Inc., Cary, NC, USA).

Results

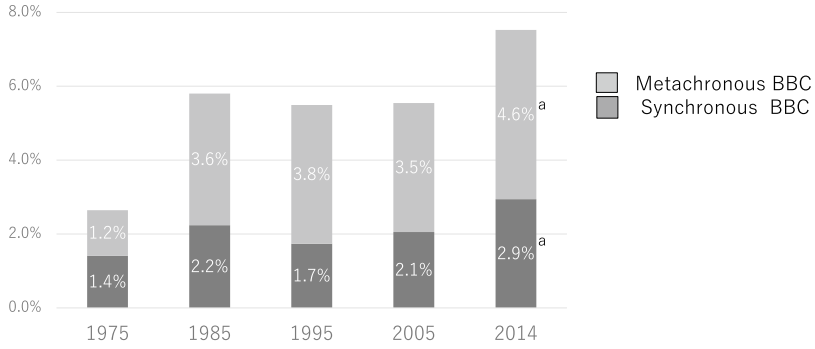
Trends of CBC incidence

The absolute number of CBC cases significantly increased over time, from 2.6% of all breast cancers in 1975 to 7.5% in 2014 ($p < 0.001$) (Fig. 2). The increase was also statistically significant in sBBC, from 1.4% in 1975 to 2.9% in 2014 ($p < 0.001$) and in mBBC, from 1.2% in 1975 to 4.6% in 2014 ($p < 0.001$).

Characteristics of bilateral breast cancers (Table 1)

Of the 11,177 women diagnosed with CBC, 4228 (37.8%) had sBBC and 6949 (62.2%) had mBBC (Table 1). Of all 22,354 cancers diagnosed in 11,177 BBC patients, 25.2% ($N = 5623$) were diagnosed at an in situ stage and 52.2% ($N = 11,679$) were diagnosed at a localized stage. With respect with histology, 14.9% ($N = 3326$) of all 11,177($\times 2$) cancers among the BBC were diagnosed with invasive lobular carcinoma or invasive lobular carcinoma mixed with other types of carcinoma, especially women with sBBC (18.1% vs. 12.9% in mBBC [$p < 0.01$]). Of the 4228 sBBC

Fig. 2 Contralateral breast cancer incidence rates



	1975	1985	1995	2005	2014
Crude Rate	2.6%	5.8%	5.5%	5.5%	7.5%[a]
All breast cancer	9418	13618	25876	60164	71505
CBC	249	790	1421	3336	5381
mBBC	133	305	450	1236	2104
sBBC	116	485	971	2100	3277

[a] $p<0.001$ Cochran-Armitage test for trend
CBC contralateral breast cancer, mBBC/sBBC metachronous/synchronous bilateral breast cancer,

Table 1 Characteristics of bilateral breast cancer

	All BBC $n=11,177\times2$		Synchronous BBC $n=4228$ (37.8%)						Metachronous BBC $n=6949$ (62.2%)					
			All sBBC		Primary tumor		Contralateral tumor (Smaller tumor)		All mBBC		Primary tumor		Contralateral tumor	
Age (years)	61.5		60.7		60.7						57.9		65.9	
Stage														
In situ	5623	25.2%	2339	27.7%	649	15.4%	1690	40.0%	3284	23.6%	1507	21.7%	1777	25.6%
Localized	11,679	52.2%	4156	49.1%	2195	51.9%	1961	46.4%	7523	54.1%	3736	53.8%	3787	54.5%
Regional	4484	20.1%	1731	20.5%	1239	29.3%	492	11.6%	2753	19.8%	1553	22.3%	1200	17.3%
Distant	462	2.1%	203	2.4%	133	3.1%	70	1.7%	259	1.9%	111	1.6%	148	2.1%
Unknown	106	0.5%	27	0.3%	12	0.3%	15	0.4%	79	0.6%	42	0.6%	37	0.5%
Surgical procedure														
BCS	9085	40.6%	2427	28.7%	1164	27.5%	1263	29.9%	6658	47.9%	3541	51.0%	3117	44.9%
Mastectomy	12,210	54.6%	5795	68.5%	2941	69.6%	2854	67.5%*	6415	46.2%	2700	38.9%	3715	53.5%*
Unknown	1059	4.7%	234	2.8%	123	2.9%	111	2.6%	825	5.9%	708	10.2%	117	1.7%
Histology														
In situ carcinoma	5715	25.6%	2373	28.1%	667	15.8%	1706	40.4%*	3342	24.0%	1537	22.1%	1805	26.0%*
DCIS	4206	18.8%	1539	18.2%	494	11.7%	1045	24.7%	2667	19.2%	1259	18.1%	1408	20.3%
DCIS + LCIS	306	1.4%	145	1.7%	46	1.1%	99	2.3%	161	1.2%	82	1.2%	79	1.1%
LCIS	1203	5.4%	689	8.1%	127	3.0%	562	13.3%	514	3.7%	196	2.8%	318	4.6%
Invasive carcinoma														
NOS	12,286	55.0%	4226	50.0%	2481	58.7%	1745	41.3%	8060	58.0%	4156	59.8%	3904	56.2%
Mucinous	334	1.5%	126	1.5%	74	1.8%	52	1.2%	208	1.5%	114	1.6%	94	1.4%
Medullary	146	0.7%	22	0.3%	11	0.3%	11	0.3%	124	0.9%	101	1.5%	23	0.3%
Lobular/mixed	3326	14.9%	1527	18.1%*	901	21.3%	626	14.8%	1799	12.9%*	836	12.0%	963	13.9%
Apocrine	53	0.2%	20	0.2%	12	0.3%	8	0.2%	33	0.2%	15	0.2%	18	0.3%
Tubular	225	1.0%	79	0.9%	28	0.7%	51	1.2%	146	1.1%	83	1.2%	63	0.9%
Papillary	57	0.3%	24	0.3%	13	0.3%	11	0.3%	33	0.2%	22	0.3%	11	0.2%
Others	197	0.9%	53	0.6%	38	0.9%	15	0.4%	144	1.0%	80	1.2%	64	0.9%
Unknown	15	0.1%	6	0.1%	3	0.1%	3	0.1%	9	0.1%	5	0.1%	4	0.1%

BBC bilateral breast cancer, *sBBC* synchronous bilateral breast cancer, *mBBC* metachronous bilateral breast cancer, *BCS* breast-conserving surgery, *DCIS* ductal carcinoma in situ, *LCIS* lobular carcinoma in situ, *NOS* not otherwise specified

*$P<0.01$

patients, 40.4% of contralateral tumors were diagnosed as in situ carcinoma compared to 26.0% of contralateral tumors of mBBC being diagnosed as in situ carcinoma ($p < 0.01$). In addition, contralateral tumors of sBBC were more likely to be treated with mastectomy than contralateral tumors of mBBC (67.5% vs. 53.5% [$p < 0.01$]).

Trends in characteristics of contralateral tumors of sBBC

The proportion of contralateral tumors of sBBC diagnosed at an early stage (in situ and localized disease) increased from 77.5% in 1975 to 89.6% in 2014 (Table 2). Contralateral tumors of sBBC were more likely to be diagnosed as in situ carcinoma than in earlier years (36.8% in 1975 and 44.3% in 2014 [$p < 0.001$]). Despite the early stage at diagnosis in most contralateral tumors in sBBC—83.5% in 1995, 84.1% in 2005 and 89.6% in 2014—mastectomy rates remained relatively high from 69.8% in 1995, 66.7% in 2005 and 69.0% in 2014.

Discussion

Our study demonstrated an increase in the number and proportion of sBBC in newly diagnosed breast cancer patients. In addition, we report findings that suggest contralateral cancers diagnosed in more recent years are more likely to be diagnosed at an earlier stage and treated with mastectomy as sBBC when compared to CBC treated in previous years. It is interesting to note that despite the fact that 90% of contralateral tumors of sBBC were detected at an early stage, nearly 70% of them were treated with mastectomy in 2014.

One of the main factors contributing to the increase of sBBC is early detection of contralateral tumors brought about by advances in breast diagnostic imaging and routine use of contralateral breast screening in patients with newly diagnosed breast cancer. Early detection of breast cancer has been conducted with a gradual shift to full-field digital mammography (FFDM) from screen film mammography

Table 2 Trends of Characteristics of Contralateral Tumors of sBBC

	1975 $n=133$		1985 $n=305$		1995 $n=450$		2005 $n=1236$		2014 $n=2104$		Value
Age (years)	56.7		62.9		65.7		65.3		67.2		
Stage											
In situ	48	36.1%	97	31.8%	131	29.1%	487	39.4%	927	44.1%	<.0001
Localized	55	41.4%	150	49.2%	245	54.4%	553	44.7%	958	45.5%	
Regional	20	15.0%	43	14.1%	64	14.2%	173	14.0%	192	9.1%	
Distant	6	4.5%	10	3.3%	8	1.8%	21	1.7%	25	1.2%	
Unknown	4	3.0%	5	1.6%	2	0.4%	2	0.2%	2	0.1%	
Surgical procedure											
BCS	3	2.3%	78	25.6%	134	29.8%	403	32.6%	645	30.7%	
Mastectomy	37	27.8%	226	74.1%	314	69.8%	825	66.7%	1452	69.0%	
Unknown	93	69.9%	1	0.3%	2	0.4%	8	0.6%	7	0.3%	
Histology											
In situ carcinoma	49	36.8%	97	31.8%	132	29.3%	496	40.1%	932	44.3%	<.0001
DCIS	22	16.5%	49	16.1%	86	19.1%	305	24.7%	583	27.7%	
DCIS + LCIS	2	1.5%	9	3.0%	7	1.6%	34	2.8%	47	2.2%	
LCIS	25	18.8%	39	12.8%	39	8.7%	157	12.7%	302	14.4%	
Invasive carcinoma											
NOS	61	45.9%	149	48.9%	218	48.4%	498	40.3%	819	38.9%	
Mucinous	3	2.3%	4	1.3%	9	2.0%	15	1.2%	21	1.0%	
Medullary	5	3.8%	4	1.3%	1	0.2%	0	0.0%	1	0.0%	
Invasive lobular/mixed	13	9.8%	43	14.1%	77	17.1%	193	15.6%	300	14.3%	
Apocrine	1	0.8%	1	0.3%	0	0.0%	3	0.2%	3	0.1%	
Tubular	1	0.8%	3	1.0%	7	1.6%	19	1.5%	21	1.0%	
Papillary	0	0.0%	2	0.7%	2	0.4%	6	0.5%	1	0.0%	
Others	0	0.0%	1	0.3%	4	0.9%	5	0.4%	5	0.2%	
Unknown	0	0.0%	1	0.3%	0	0.0%	1	0.1%	1	0.0%	

BCS breast-conserving surgery, *DCIS* ductal carcinoma in situ, *LCIS* lobular carcinoma in situ, *NOS* not otherwise specified

[4]. As FFDM replaced analog mammography, some reports revealed that breast cancer associated with microcalcifications often associated with DCIS was more likely to be identified by FFDM [5]. As a result, the incidence of DCIS has markedly increased from 5.83/100,000 women in 1975 to 37.02/100,000 in 2009 based on November 2016 SEER data [6]. Contralateral breast screening has been conducted with mammography since the 1990s; compared with clinical breast examination alone, mammography resulted in a 2.4 increase in the number of breast cancers detected [7, 8]. In addition, the use of breast magnetic resonance imaging (MRI) might contribute to the increase in sBBC incidence. Currently in the United States, MRI is frequently used for estimating extent of disease even in those without an inherited predisposition to breast cancer. MRI technology has a high sensitivity for detecting breast cancer [9]. Advances in MRI equipment have enabled simultaneous screening of the contralateral breast as well as the ipsilateral site. It has been reported that MRI can detect mammographically and clinically occult contralateral breast cancer in 3.1% of women with unilateral breast cancer [10]. Although the details of these changes in imaging modalities were not coded in the SEER database, these advancements in mammography and MRI likely have had a substantial impact on the early detection of CBC.

It has also been postulated that one of the causes of the increasing sBBC rates in the United States is the growing number of occult cancers diagnosed after a contralateral prophylactic mastectomy (CPM). The proportion of unilateral breast cancer patients who undergo CPM have increased from 3.9% in 2002 to 12.7% in 2012 [11], and the incidence rate of occult breast cancer diagnosed after CPM ranges between 1.3 and 11.3% [12–16]. Detecting occult cancer in CPM specimens is likely to be an additional reason for the increase of contralateral tumors of sBBC.

It is noteworthy and not surprising that many sBBC patients chose mastectomy for their contralateral breast tumors despite its early detection. Although sBBC is not an absolute contraindication for breast-conserving surgery [17] and even after 1991 when a National Institutes of Health consensus statement recommended breast-conserving surgery plus radiation as an appropriate alternative primary therapy to mastectomy for the majority of women with early stage breast cancer [18], our result showed that about 70% of contralateral tumors of sBBC were treated with mastectomy in 1995, 2005, and 2014, despite 83–90% of contralateral tumors being diagnosed at an early stage (Table 2). Importantly, our analyses excluded data from 1975 to 1985, as the majority of breast surgery was mastectomy in this era; thus, these results reflect trends in the breast conservation era from 1995 to 2014. Explanations surrounding why women diagnosed with CBC are choosing mastectomy over breast-conserving surgery are complex and unclear. Several studies suggest that BBC is one of the related clinical factors that increases the probability of BRCA mutations [19, 20] and remains one of the criteria for recommendation of genetic testing [17]. In the absence of a genetic predisposition, the presence of the second breast cancer may also motivate patients to choose a more aggressive surgical approach that will reduce their overall breast cancer risk in the future.

In addition to these explanations, one could also posit that surgeons would have been more apt to recommend bilateral mastectomy for BBC patients, particularly for lobular cancers. It is well known that invasive lobular carcinomas have a higher frequency of bilaterality and multicentricity than invasive ductal carcinomas [21]. Patients with invasive lobular carcinoma or invasive lobular carcinoma mixed with other types of carcinoma were significantly more likely to undergo mastectomy than invasive ductal carcinoma not otherwise specified in both sBBC and mBBC (Table 3). Although invasive lobular carcinoma represents 10–15% of invasive breast tumors [22], our study showed that 20.0% of invasive BBC cases were invasive lobular carcinoma and infiltrating lobular carcinoma mixed with other types of carcinoma. In addition, of the sBBC patients, 21.3% of the primary tumors were diagnosed with invasive lobular carcinoma compared to 14.8% of the contralateral tumors (Table 1). Although there are possibilities that the patients diagnosed with invasive lobular carcinoma had more aggressive imaging, diagnostic intervention and prophylactic treatment for the contralateral breast, we could not assess the details in SEER data.

sBBC incidence can be approximated according to how many patients with CBC are treated simultaneously among the total number of patients with primary breast cancer during the same period. Similar estimates of mBBC incidence in this study were approximated by calculating how many patients had a previous CBC among the number of

Table 3 Association between Invasive lobular carcinoma and mastectomy for sBBC and mBBC

	Contralateral tumors of sBBC			Contralateral tumors of mBBC		
Histology	Mastectomy	Total	P	Mastectomy	Total	P
Lobular/mixed	461 (73.6%)	626	< 0.001	582 (60.4%)	963	< 0.001
NOS	1138 (60.4%)	1745		2106 (53.9%)	3904	

BCS breast-conserving surgery, *sBBC* synchronous bilateral breast cancer, *mBBC* metachronous bilateral breast cancer, *NOS* not otherwise specified

patients with primary breast cancer during the same periods. On the other hand, the incidence of mBBC generally expresses the future risk of CBC for unilateral breast cancer patients and is estimated by how often CBC occurs during follow-up for a unilateral breast cancer. In previous reports using a large database, the overall trend of mBBC was found to be declining, possibly because of the widespread usage of adjuvant hormonal therapies [23, 24]. As shown in this study, although the chance of finding mBBC may have increased due to the number of patients treated with unilateral breast cancer and advances in diagnostic imaging, the risk of CBC is also expectedly reduced by appropriate systemic treatment.

Our study has several limitations inherent to large data sets. The SEER database lacks information on the diagnostic imaging techniques utilized, patient family histories or genetic predispositions, HER2 status, systemic therapies administered, and details of the surgical procedures performed; therefore, we could not adjust for these factors to understand the detailed relationship with BBCs. Nonetheless, this large-scale study with over 10,000 CBC with clinicopathologic data of each side which is difficult to extract from other sources provided a unique opportunity to assess temporal trends of sBBC incidence.

In summary, our study reveals that in the United States, the number of sBBC has been increasing and contralateral tumors are more likely to be diagnosed at an early stage and treated with mastectomy. As breast diagnostic imaging becomes more widely and routinely available for contralateral breast screening, the increase in sBBC incidence may be seen in other countries as well. Although most women with CBC chose mastectomy, future studies are needed to demonstrate the clinical significance of early detection of contralateral tumors and optimal screening and surveillance methods.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval This study was epidemiological study using de-identified data from the SEER database. Therefore, consent for patient participation and study publication was not required. Because this study did not meet the definition of human subject research, the protocol was considered exempt from review from the Dana-Farber Cancer Institute Institutional Review Board (DFCI Protocol No.: 18-034).

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