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ORIGINAL ARTICLE – BREAST ONCOLOGY

Risk of Contralateral Breast Cancer in Women with Ductal Carcinoma In Situ Associated with Synchronous Ipsilateral Lobular Carcinoma In Situ

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ABSTRACT

Background. Lobular carcinoma in situ (LCIS) is a risk factor for breast cancer, but the effect of LCIS found in association with ductal carcinoma in situ (DCIS) is unknown. In this study, we compared contralateral breast cancer (CBC) and ipsilateral breast tumor recurrence (IBTR) rates among women with DCIS with or without synchronous ipsilateral LCIS treated with breast-conserving surgery (BCS).

Methods. DCIS patients undergoing BCS from 2000 to 2011 with a contralateral breast at risk were stratified by the presence or absence of synchronous ipsilateral LCIS with the index DCIS (DCIS + LCIS vs. DCIS). Those with contralateral, bilateral, or prior ipsilateral LCIS were excluded. Associations of patient, tumor, and treatment factors with CBC and IBTR were evaluated.

Results. Of 1888 patients identified, 1475 (78%) had DCIS and 413 (22%) had DCIS + LCIS. At median follow-up of 7.2 (range 0–17) years, 307 patients had a subsequent first breast event; 207 IBTR and 100 CBC. The 10-year cumulative incidence of IBTR was similar in both groups: 15.0% vs. 14.2% (log-rank, $p = 0.8$) for DCIS + LCIS vs. DCIS, respectively. The 10-year cumulative incidence of CBC was greater in the DCIS + LCIS group: 10.9% vs. 6.1% for DCIS (log-rank, $p < 0.001$). After adjustment for other factors, CBC risk remained higher in DCIS + LCIS compared with DCIS (hazard ratio 2.06, 95% confidence interval 1.36–3.11, $p = 0.001$); there was no significant difference in IBTR risk.

Conclusions. Compared with DCIS alone, DCIS + LCIS is associated with similar IBTR risk but double the risk of CBC. This finding should inform treatment decisions, in particular regarding endocrine therapy for risk reduction.

Lobular carcinoma in situ (LCIS) is a risk factor for the development of breast cancer. Women with LCIS have an annual incidence of breast cancer of 1–2% and a relative risk that exceeds that in the general population by three- to 10-fold.[1–6] Breast cancer risk is elevated in both the ipsilateral and contralateral breast, and tends to present at an early stage.[5–7]

Less is known about the effect of LCIS on breast cancer risk in the setting of a concurrent diagnosis of breast cancer. Previous studies in women with early-stage breast cancer and LCIS undergoing breast-conserving therapy have demonstrated variable results regarding the risk of ipsilateral breast tumor recurrence (IBTR), ranging from no difference to double the risk of recurrence with the presence of LCIS.[8–14] However, the majority of these series focused on risk of IBTR rather than incidence of contralateral breast cancer (CBC).

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The risk of developing CBC for average-risk women with breast cancer is low, estimated to range from 0.1 to 0.6% per year, and has decreased in recent years.[15–19] Recent studies of CBC risk in patients with DCIS demonstrate a cumulative incidence of 2.5–3.2% at 5 years and 6.4–6.8% at 10 years following breast-conserving surgery (BCS), confirming that the risk of CBC is also low in patients with pre-invasive breast cancer.[20,21] While these studies assessed patient, treatment, and DCIS characteristics, they did not include LCIS as a potential risk factor for CBC.

Despite the known predisposition to breast cancer associated with LCIS, the effect of LCIS diagnosed concurrently with DCIS on the risk of CBC is not known. In this study, we sought to compare CBC and IBTR rates in women with DCIS with and without synchronous ipsilateral LCIS treated with BCS.

METHODS

Following institutional review board approval, all patients with a contralateral breast at risk for the subsequent development of breast cancer were identified from a prospectively maintained database of DCIS patients treated with BCS at Memorial Sloan Kettering Cancer Center (MSK) from 2000 to 2011. Patients were stratified into two groups by the presence of LCIS in either the core needle biopsy or the surgical excision specimen of the index DCIS (DCIS + LCIS), or by the absence of LCIS in both (DCIS). Those with contralateral, bilateral, or previous ipsilateral LCIS were excluded. All patients underwent surgery at MSK, and their core needle and surgical specimens were examined by MSK pathologists.

Clinicopathologic factors were collected based on the index DCIS, including age at diagnosis, family history of breast cancer (1 or more first- or second-degree relatives), presentation (radiologic or clinical), nuclear grade (low or intermediate/high), number of excisions required (≤ 2 or ≥ 3), margin status (positive/close [≤ 2 mm] or negative [> 2 mm]), and use of adjuvant radiation and endocrine therapy for the index DCIS. Cases of markedly atypical ductal hyperplasia bordering on or focally reaching DCIS were included as low-grade DCIS. A random sample of 10% of cases for each year were re-reviewed by a single pathologist (D.G.) to ensure the "DCIS-only" group comprised solely patients without LCIS.

The primary endpoint was time from definitive surgery for the index DCIS to diagnosis of a first subsequent event, whether IBTR or CBC. A diagnosis of either DCIS or invasive breast cancer was considered an event. IBTR included ipsilateral recurrence in the breast or axilla. For IBTR, patients were censored at the time of CBC or contralateral prophylactic mastectomy (CPM), or at the time of last follow-up if no event had occurred. Similarly, for CBC, patients were censored at the time of IBTR, CPM, or last follow-up.

One minus the Kaplan–Meier estimate was used to obtain the 5- and 10- year cumulative incidence of CBC and IBTR. Competing risk analysis was used to compare the risk of CBC with that of IBTR. Differences in CBC and IBTR rates by the presence of LCIS were assessed using the log-rank test. A separate competing risks analysis for type of recurrence (invasive vs. DCIS) was performed for CBC and IBTR; Gray's test was used to compare the cumulative incidence of recurrence type by LCIS status.

Differences in clinicopathologic features were compared between the DCIS-only and DCIS + LCIS groups using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Univariable and multivariable Cox regression models evaluated associations between CBC and IBTR, and each clinicopathologic factor, including the presence of LCIS. Interactions between LCIS presence and each covariate were examined for both outcomes using likelihood ratio tests, none of which were found to be statistically significant, and thus not incorporated into the final multivariable models. A p value < 0.05 was considered statistically significant. All statistical analyses were performed in R software version 3.5.0 (R Core Development Team, Vienna, Austria), including use of the "survival" package.

RESULTS

From 2000 to 2011, there were 1888 DCIS patients who underwent BCS with a contralateral breast at risk. Of these, 1475 (78%) had DCIS only and 413 (22%) had DCIS + LCIS. The median patient age was 57 (range 20–93) years. Characteristics and treatment of the index DCIS for the entire population, and by presence of LCIS, are summarized in Table 1. More than 90% were diagnosed radiologically, and 40% had a family history of breast cancer in at least one first- or second-degree relative. Receipt of adjuvant radiation and endocrine therapy was similar in both the DCIS and DCIS + LCIS groups.

Median follow-up among event-free patients was 7.2 (range 0–17) years; 463 patients had ≥ 10 years of follow-up. 307 patients had a subsequent breast event; 207 developed IBTR first and 100 developed CBC first. Two patients were diagnosed with subsequent IBTR and CBC on the same date and included as events for both outcomes. Of the 207 patients who developed IBTR, 98 (47.3%) were invasive and 108 (52.2%) were DCIS. The type of IBTR was unknown in one case. Of the 100 CBCs, 66 (66.0%) were invasive and 34 (34.0%) were DCIS.

TABLE 1 Demographic characteristics of the entire population and in those with DCIS associated with synchronous ipsilateral LCIS compared with DCIS only

	Total population $n = 1888$		DCIS + LCIS $n = 413$		DCIS only $n = 1475$		p value*
	n or median	% or range	n or median	% or range	n or median	% or range	
Age (years)	56.6	20.1–92.6	55.3	34.1–87.8	56.7	20.1–92.6	0.72
Family history							1.00
No	1110	58.8	242	58.6	868	58.8	
Yes	761	40.3	166	40.2	595	40.3	
Unknown	17	0.9	5	1.2	12	0.8	
Presentation							0.16
Clinical	157	8.3	27	6.5	130	8.8	
Radiologic	1731	91.7	386	93.5	1345	91.2	
Nuclear grade							0.84
Low	410	21.7	91	22.0	319	21.6	
Intermediate/high	1458	77.2	317	76.8	1141	77.4	
Unknown	20	1.1	5	1.2	15	1.0	
Radiation							0.26
No	755	40.0	175	42.4	580	39.3	
Yes	1122	59.4	235	56.9	887	60.1	
Unknown	11	0.6	3	0.7	8	0.5	
Endocrine therapy							0.41
No	1479	78.3	317	76.8	1162	78.8	
Yes	393	20.8	92	22.3	301	20.4	
Unknown	16	0.8	4	1.0	12	0.8	
Margin status							0.73
Negative (> 2 mm)	1657	87.8	360	87.2	1297	87.9	
Positive/close (≤ 2 mm)	229	12.1	52	12.6	177	12.0	
Unknown	2	0.1	1	0.2	1	0.1	
Number of excisions							0.83
≤ 2	1745	92.4	380	92.0	1365	92.5	
≥ 3	142	7.5	32	7.7	110	7.5	
Unknown	1	0.1	1	0.2	0	0.0	

DCIS ductal carcinoma in situ; *LCIS* lobular carcinoma in situ

*p value comparing DCIS + LCIS vs. DCIS only groups. Fisher's exact test was used for categorical variables, and the Wilcoxon rank-sum test was used for continuous variables

On competing risk analysis for recurrence as DCIS versus invasive cancer, there was no significant difference in whether either CBC or IBTR presented as DCIS or invasive disease between the DCIS + LCIS and DCIS-only groups.

Ipsilateral Breast Cancer Risk

The 5- and 10-year cumulative incidence of IBTR was similar in both groups: 6.3% and 14.2% for DCIS-only compared with 6.1% and 15.0% for DCIS + LCIS, respectively (log-rank, $p = 0.8$; Fig. 1). On univariable analysis, the risk of IBTR was lower in those receiving radiation (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.52–0.90, $p = 0.007$) or endocrine therapy (HR 0.48, 95% CI 0.33–0.71, $p < 0.001$), and higher in those requiring more excisions (HR 1.64, 95% CI 1.09–2.46, $p = 0.016$; Table 2). On multivariable analysis, use of radiation and endocrine therapy and fewer excisions remained significantly associated with lower risk of IBTR. Patients with intermediate- or high-grade DCIS compared with low-grade disease (HR 1.58, 95% CI 1.08–2.31,

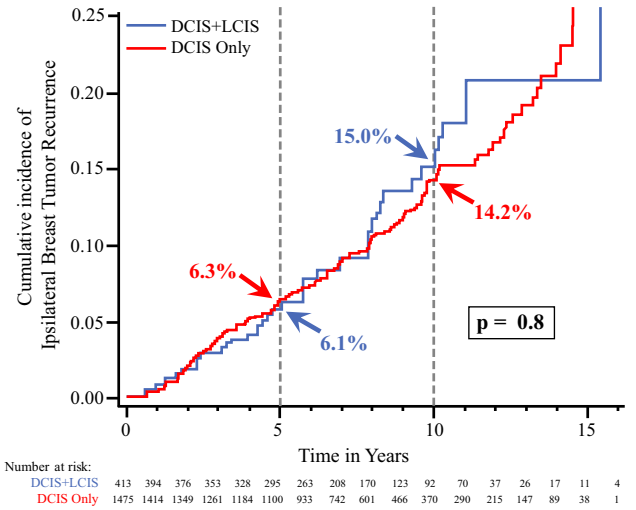

FIG. 1 Cumulative incidence of ipsilateral breast tumor recurrence after breast-conserving surgery for DCIS with synchronous ipsilateral LCIS compared with DCIS alone. *DCIS* ductal carcinoma in situ; *LCIS* lobular carcinoma in situ

$p = 0.02$), and those who presented clinically versus radiologically (HR 1.57, 95% CI 1.04–2.38, $p = 0.03$) also had a higher risk of IBTR on multivariable analysis. The presence of LCIS was not significantly associated with IBTR on either univariable or multivariable analysis.

Contralateral Breast Cancer Risk

The 5- and 10-year cumulative incidence of CBC was greater in the DCIS + LCIS group: 5.7% and 10.9%, compared with 2.9% and 6.1% for DCIS-only, respectively (log-rank, $p < 0.001$; Fig. 2). On univariable analysis, older age, intermediate- or high-grade disease, lack of endocrine therapy, and LCIS + DCIS were all significantly associated with increased risk of CBC (Table 3). On multivariable analysis, CBC risk was two-fold higher in the DCIS + LCIS group compared with the DCIS-only group (HR 2.06, 95% CI 1.36–3.11, $p = 0.001$). Receipt of endocrine therapy was the only other factor significantly associated with CBC on multivariable analysis (HR 0.44, 95% CI 0.24–0.79, $p = 0.001$).

DISCUSSION

With DCIS accounting for 20% of breast cancers diagnosed annually in women in the United States, concerns exist regarding both overtreatment and undertreatment of this pre-invasive lesion.[22] Recent attention has also focused on the contribution of atypical breast lesions, and in particular LCIS, to breast cancer risk. While LCIS is an established risk factor for breast cancer, the effect of LCIS on subsequent breast events when identified in association with DCIS has not been well defined. In the current era of personalized medicine, it is increasingly important to understand the biology and behavior of each patient's diagnosis to guide treatment decisions.

Our goal was to better understand the risk of CBC and IBTR in women undergoing BCS for DCIS with associated LCIS. In our cohort of 1888 patients with DCIS, nearly one-quarter were diagnosed with synchronous ipsilateral LCIS. The cumulative incidence of IBTR did not differ significantly based on the presence of LCIS. However, the cumulative incidence of CBC in the group with concurrent DCIS and LCIS was nearly twice that found in the group with DCIS only, 5.7% and 10.9%, compared with 2.9% and 6.1% at 5 and 10 years, respectively. On multivariable analysis that adjusted for six clinicopathologic and treatment factors, the presence of LCIS remained associated with a two-fold increase in CBC risk.

Previous studies in women with early-stage breast cancer and LCIS have shown variable associations between the presence of LCIS and IBTR following breast-conserving therapy. Sasson et al. found that in women with early-stage invasive breast cancer treated between 1979 and 1995, the rate of IBTR was 15% (10/65) in patients with concurrent LCIS compared with 5% (57/1209) in patients without LCIS ($p = 0.001$).[14] Similarly, LCIS was independently associated ($p = 0.02$) with a higher rate of IBTR in 607 patients with invasive breast cancer treated from 1980 to 1996, although only 56 (9%) had concurrent LCIS.[11] In a study specifically examining patients with DCIS and proliferative breast lesions treated from 1991 to 1995, the cumulative IBTR rate was twice as high in those with DCIS and lobular neoplasia when compared to patients with DCIS alone ($p = 0.002$).[23] Consistent with our results, another large, single-institution series found that the presence of LCIS in the surgical specimen, including at the margin, was not associated with IBTR in 2894 patients with early-stage breast cancer treated with BCS from 1980 to 2007.[9] Similarly, a Danish national prospective study of DCIS patients treated with excision alone from 1982 to 1989 demonstrated a similar rate of invasive IBTR for those with and without concurrent LCIS.[13] Adepoju and colleagues reported no significant difference in IBTR rates among women with DCIS with or without proliferative lesions and, similar to our results, did find a higher risk of CBC associated with DCIS and concurrent high-risk lesions (actuarial CBC rate at 15 years: 19.9% DCIS + atypical hyperplasia/LCIS vs. 4.3% DCIS alone, $p = 0.023$).[8]

The differences in IBTR rates reported in earlier studies are partially explained by the variable inclusion of patients with invasive disease, DCIS, and LCIS, with and without other proliferative lesions, making direct comparison to our study difficult. Uniquely, our cohort includes only patients

TABLE 2 Univariable and multivariable Cox regression analysis of characteristics at initial diagnosis of DCIS as risk factors for ipsilateral breast tumor recurrence

	Univariable analysis			Multivariable analysis		
	IBTR HR	95% CI	*p* value	IBTR HR	95% CI	*p* value
Age (continuous)	0.99	0.98–1.0	0.11	0.99	0.98–1.00	0.06
Family history						
No	1.00			1.00		
Yes	1.06	0.81–1.41	0.66	1.12	0.84–1.48	0.45
Presentation						
Radiologic	1.00			1.00		
Clinical	1.45	0.96–2.19	0.08	1.57	1.04–2.38	0.03
Grade						
Low	1.00			1.00		
Intermediate/high	1.31	0.92–1.87	0.14	1.58	1.08–2.31	0.02
Radiation						
No	1.00			1.00		
Yes	0.69	0.52–0.90	0.007	0.59	0.43–0.79	0.001
Endocrine therapy						
No	1.00			1.00		
Yes	0.48	0.33–0.71	< 0.001	0.51	0.34–0.75	0.001
Margin status						
Negative (> 2 mm)	1.00			1.00		
Positive/close (≤ 2 mm)	1.26	0.85–1.87	0.24	1.37	0.92–2.04	0.12
Number of excisions						
≤ 2	1.00			1.00		
≥ 3	1.64	1.09–2.46	0.016	1.84	1.21–2.80	0.004
DCIS without/with synchronous ipsilateral LCIS						
DCIS only	1.00			1.00		
DCIS + LCIS	1.05	0.76–1.46	0.76	1.07	0.77–1.49	0.70

DCIS ductal carcinoma in situ; *LCIS* lobular carcinoma in situ; *IBTR* ipsilateral breast tumor recurrence; *HR* hazard ratio; *CI* confidence interval

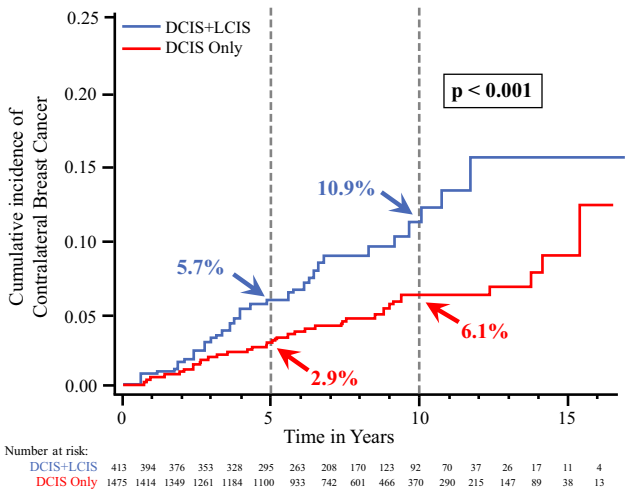

FIG. 2 Cumulative incidence of contralateral breast cancer after breast-conserving surgery for DCIS with synchronous ipsilateral LCIS compared with DCIS alone. *DCIS* ductal carcinoma in situ; *LCIS* lobular carcinoma in situ

with DCIS with or without synchronous ipsilateral LCIS. Furthermore, our patients were treated in 2000 or later, thereby reflecting contemporary management strategies. Additionally, all core biopsy and surgical specimens in our study were examined by MSK pathologists, and 10% were re-reviewed to ensure accurate histologic classification. These differences in patient selection and methodology may account for the variation in IBTR rates in the groups with and without LCIS between ours and previous series.

On multivariable analysis, we found that clinical presentation, intermediate/high-grade DCIS, and three or more excisions were significantly associated with IBTR—risk factors that are consistent with prior literature.[23–29] Consistent with results from the large, prospective, randomized trials demonstrating that radiation and endocrine therapy decrease IBTR by approximately 50% and 30%,

TABLE 3 Univariable and multivariable Cox regression analysis of characteristics at initial diagnosis of DCIS as risk factors for subsequent contralateral breast cancer

	Univariable analysis			Multivariable analysis		
	CBC HR	95% CI	*p* value	CBC HR	95% CI	*p* value
Age (continuous)	1.02	1.00–1.04	0.02	1.02	1.0–1.04	0.05
Family history						
No	1.00			1.00		
Yes	1.21	0.81–1.80	0.35	1.23	0.83–1.85	0.31
Presentation						
Radiologic	1.00			1.00		
Clinical	0.66	0.29–1.52	0.33	0.74	0.33–1.70	0.49
Grade						
Low	1.00			1.00		
Intermediate/high	1.91	1.07–3.42	0.03	1.79	0.97–3.29	0.06
Radiation						
No	1.00			1.00		
Yes	1.20	0.80–1.82	0.38	1.12	0.71–1.75	0.63
Endocrine therapy						
No	1.00			1.00		
Yes	0.45	0.25–0.81	0.006	0.44	0.24–0.79	0.001
Margin status						
Negative (> 2 mm)	1.00			1.00		
Positive/close (≤ 2 mm)	1.15	0.64–2.06	0.64	1.07	0.59–1.93	0.83
Number of excisions						
≤ 2	1.00			1.00		
≥ 3	1.27	0.66–2.44	0.48	1.32	0.67–2.57	0.42
DCIS without/with synchronous ipsilateral LCIS						
DCIS only	1.00			1.00		
DCIS + LCIS	1.98	1.31–2.99	0.001	2.06	1.36–3.11	0.001

DCIS ductal carcinoma in situ; *LCIS* lobular carcinoma in situ; *CBC* contralateral breast cancer; *HR* hazard ratio; *CI* confidence interval

respectively, both adjuvant therapies were associated with a lower risk of IBTR (HR 0.59, $p = 0.001$ for radiation; HR 0.51, $p = 0.001$ for endocrine therapy) in our study.[30–34]

The low incidence of CBC in the group of patients with DCIS alone observed in the current data is similar to those in prior studies. In the literature reporting on risk of CBC among women with DCIS, rates of CBC are 2.5–4.3% at 5 years and 6.0–6.8% at 10 years.[16,20,21,35,36] Given that women with a history of LCIS are at increased risk for developing breast cancer in either breast, we hypothesized that the incidence of CBC in patients with DCIS + LCIS would exceed that in patients with DCIS alone. On multivariable analysis, patients with synchronous DCIS and LCIS had double the risk of CBC compared with patients with DCIS alone (HR 2.06, $p = 0.001$).

In our cohort, after adjustment for multiple factors on multivariable analysis, use of endocrine therapy for the index DCIS was associated with a 56% lower risk of CBC (HR 0.44, $p = 0.001$). This is consistent with the two randomized studies that examined the use of tamoxifen in women undergoing BCS for DCIS, which found a 32% (NSABP B-24) and 56% (UK-ANZ trial) reduction in CBC.[31,33]

The use of endocrine therapy for adjuvant treatment in women with DCIS in the modern era is relatively low. In our cohort, 21% of patients who underwent BCS for DCIS received tamoxifen or an aromatase inhibitor; the uptake rate did not differ based on presence of concurrent LCIS. Among 206,255 patients in the National Cancer Database with DCIS diagnosed between 2005 and 2012, the use of adjuvant endocrine therapy was 36.5%.[37] This is somewhat surprising given the evidence from large, prospective randomized trials demonstrating the efficacy of endocrine therapy in preventing both ipsilateral and contralateral subsequent breast events in women with DCIS.[27,30,31,33] Variability in the uptake and adherence to endocrine

therapy reflect perception of the overall excellent prognosis for women with DCIS, adverse effects associated with endocrine therapy medications, and physician recommendations regarding its use.[38–40] Increasing patient age and lack of insurance have been associated with reduced compliance, whereas receipt of adjuvant radiation and care provided in a multidisciplinary setting are correlated with increased uptake.[38,41] Adjuvant therapy for women undergoing BCS for DCIS aims to minimize the risk of recurrence while avoiding overtreatment for a pre-invasive lesion. This balance is complex, incorporating both pathologic and patient features, and tolerance of risk. Studies have shown that patients with "low-risk" DCIS (i.e., low grade, screen detected, and/or small volume) have lower absolute IBTR rates compared with higher-risk lesions but that adjuvant therapy still provides an absolute reduction in recurrence risk.[21,42,43] It is therefore important to educate patients on all available risk factors for future breast cancer events so that informed decision making is possible.

Our study demonstrated a significantly higher cumulative incidence of CBC in patients with DCIS and synchronous LCIS undergoing BCS, confirming that LCIS is a risk factor for CBC in the setting of ipsilateral DCIS. Importantly, endocrine therapy was associated with a lower risk of both IBTR and CBC among this population of women with DCIS. Combined with previous evidence demonstrating the benefit of chemoprevention in patients with LCIS, our results indicate that endocrine therapy should be considered for both treatment of the index DCIS and prevention of subsequent CBC in women with synchronously diagnosed LCIS. Given the low uptake rates of endocrine therapy, greater attention to counseling patients regarding the risk-reduction benefits of tamoxifen and aromatase inhibitors is needed. Furthermore, in the current era of concern regarding the overtreatment of DCIS, the presence of LCIS can be used as an additional risk factor to aid in decision making and personalize therapy for women with DCIS.

Our study was retrospective in nature and subject to all associated limitations. The use of radiation and endocrine therapy were determined by the treating physician and patient, and reflect perceived risk of recurrence. Although estrogen receptor (ER) status was not available, the majority of DCIS is ER positive, and other large, prospective studies demonstrating the benefit of endocrine therapy for DCIS enrolled patients without knowledge of hormone receptor status.[31,33,37] Information regarding receipt of genetic testing or genetic testing results was not available and therefore could not be included in the analysis. However, our detailed, prospectively maintained database, including annotated clinicopathologic data, allowed multivariable analysis to adjust for potentially confounding factors that could affect risk. While assessment of the volume of LCIS or its presence at the margins of resection was not possible, MSK pathology review and re-review of 10% of the cohort confirmed the diagnosis of LCIS to a degree not possible in other retrospective studies which relied on pathology reports. In addition, our patient population represents a large group of women with DCIS eligible for BCS and includes a more contemporary cohort than previous studies examining the risk of CBC.

In summary, our data provide an assessment of the incidence of subsequent breast events in the setting of concurrently diagnosed DCIS + LCIS to help to individualize treatment recommendations. Patients with DCIS and synchronously diagnosed LCIS represent a unique group at elevated risk of CBC after BCS, although the presence of LCIS did not affect subsequent IBTR. Endocrine therapy was associated with lower risk of both CBC and IBTR. A balanced discussion regarding the risks and benefits of treatment options for women with DCIS + LCIS should include the use of endocrine therapy for management of both the index DCIS and to prevent future CBC.

CONCLUSIONS

DCIS diagnosed with synchronous ipsilateral LCIS has twice the risk of CBC compared with DCIS alone. This should inform treatment decisions, in particular regarding endocrine therapy for risk reduction.

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