# Prognostic Significance of Lobular Carcinoma In-Situ (LCIS) Diagnosed Alongside Invasive Breast Cancer

Maxwell C Braasch[1], Amanda L Amin[2], Christa R Balanoff[2], Jamie L Wagner[2] and Kelsey E Larson[2]

[1]School of Medicine, The University of Kansas Health System, Kansas City, KS, USA. [2]Division of Breast Surgery, Department of Surgery, The University of Kansas Health System, Kansas City, KS, USA.

Breast Cancer: Basic and Clinical Research
Volume 16: 1–5

DOI: 10.1177/11782234211070217
SAGE

## ABSTRACT

**PURPOSE:** Women with lobular carcinoma in-situ (LCIS) have an increased risk for developing breast cancer (BC) compared with the general population. However, little is known about the clinical implication of diagnosing LCIS concurrently with an invasive breast cancer. We aimed to define the rate of LCIS diagnosed concurrently with an invasive breast cancer and investigate the risk of contralateral breast cancer (CBC) during survivorship care.

**MATERIALS AND METHODS:** A single center retrospective review over 6 years identified women with stage I-III BC who underwent lumpectomy or unilateral mastectomy. Patients with or without concurrent LCIS were compared using Chi-squared analyses to assess for differences in clinicopathologic factors and risk of future CBC (including invasive and in-situ disease).

**RESULTS:** Of 1808 patients, 16.6% (n = 301) had LCIS concurrent with their index breast cancer. Patients with LCIS had a higher rate of subsequent CBC development than those without LCIS (3.3% versus 1.0%, $P = .004$). The risk ratio for patients with LCIS developing subsequent CBC compared with those without LCIS was 3.3 (95% confidence interval [CI]: 1.5-7.3).

**CONCLUSIONS:** Patients with LCIS diagnosed concurrently with their index breast cancer at surgery are at higher risk for subsequent CBC than those without LCIS. The evidence from this study suggest that it may be appropriate for women with LCIS diagnosed alongside an index breast cancer to consider on-going high-risk screening during survivorship care.

**KEYWORDS:** Breast neoplasms, risk assessment, risk factors, cancer survivors

**RECEIVED:** August 5, 2021. **ACCEPTED:** October 19, 2021.

**TYPE:** Original Research

**FUNDING:** The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors thank Holly R. Zink, MSA of the Department of Surgery, University of Kansas, Kansas City, KS, for providing medical writing and editorial support for this research along with Dr. G. John Chen of the Department of Surgery, University of Kansas, Kansas City, KS for providing statistical support for this research.

**DECLARATION OF CONFLICTING INTERESTS:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**CORRESPONDING AUTHOR:** Kelsey E Larson, Division of Breast Surgery, Department of Surgery, The University of Kansas Health System, 4000 Cambridge Street, Kansas City, KS 66160, USA. Email: klarson6@kumc.edu

## Introduction

Lobular carcinoma in situ (LCIS) is a non-malignant high-risk lesion of the breast which indicates an increased risk of index breast cancer development.[1-3] Women with LCIS have up to 40% lifetime risk documented in prior studies.[3-6] Due to this increased risk, patients diagnosed with LCIS are eligible for high-risk screening which includes yearly mammogram plus yearly magnetic resonance imaging (MRI) or ultrasound.[7] Moreover, chemoprevention may be appropriate in select patients to reduce the risk of breast cancer development.[2,7,8]

While it is known that LCIS increases the risk of an index breast cancer, the clinical implication and prognostic value of diagnosing LCIS concurrently with an invasive breast cancer is unknown.[1,3] The rate of LCIS identified concurrently with an index breast cancer varies from 4.8% to 22% in the literature.[9-14] A single prior study reported a higher rate of contralateral breast cancer (CBC) in patients with ductal carcinoma in situ (DCIS) and concurrent LCIS, but similar data on patients with invasive breast cancer is lacking.[14] Due to a paucity of data, the current clinical management of invasive breast cancer patients does not take into account the presence or absence of LCIS when considering survivorship and follow-up recommendations.

This study aimed to define the rate of LCIS diagnosed concurrently with an invasive breast cancer, and to investigate the risk of CBC in these patients during survivorship care. The results may affect clinical protocols by guiding survivorship patient management and care in this subgroup.

## Materials and Methods

Following Institutional Review Board (IRB) approval, electronic medical records were accessed to identify patients > 18 years old diagnosed with stages I to III breast cancer treated with lumpectomy or unilateral mastectomy at our institution between January 2013 to April 2019. Patients who underwent neoadjuvant chemotherapy or endocrine therapy were excluded, including those with a diagnosis inflammatory breast cancer. Our institution is an NCI-Designated Center and as such all patients in this study received care from dedicated breast surgical oncologists along with breast-specific radiologists, pathologists, and radiation oncologists.

*Demographics and clinicopathological characteristics*

Variables recorded included patient demographic characteristics, medical insurance type (private/Medicare/Medicaid), family history of breast cancer or ovarian cancer; personal history of LCIS (ipsilateral/contralateral), personal history of atypia (ipsilateral/contralateral), BRCA1/2 positive results, breast cancer histologic type (invasive ductal/invasive lobular, breast cancer operation type (lumpectomy/unilateral mastectomy), breast cancer treatment (adjuvant endocrine therapy/adjuvant radiation/declined radiation (lumpectomy), and the average years of patient follow-up. Clinicopathological details such as follow-up time and subsequent CBC diagnosis were documented. For CBC, both invasive and in-situ disease was included as CBC diagnosis. No cancer-specific disease details were collected as these factors have not been shown to impact CBC development so were irrelevant to our aims. Factors such as endocrine therapy and genetic results which could impact risk of future CBC were collected to ensure they were included in the data analysis as potential confounding variables. The pathological, oncological, and radiology databases were reviewed for all patients to ensure completeness of data.

*Statistical analysis*

Study patients were separated into two groups for statistical analysis based on the presence or absence of LCIS concurrent with the index breast cancer in their surgical pathology specimen. The two groups were compared using chi-squared and two-tailed *t*-tests, chi-squared, and relative risk analyses were also performed to assess for an association between cohorts with respect to future CBC development. Statistical significance was defined as *P*-value of $< .05$.

## Results

In our overall cohort of 1808 patients, 301 (16.6%) had LCIS identified in their surgical specimen (Table 1). The majority of LCIS was classic type with only five (0.2%) patients having pleomorphic LCIS. Cohorts were similar with respect to demographics, family history of breast cancer, personal history of LCIS or atypia prior to their index breast cancer, and adjuvant endocrine therapy use. Patients with LCIS were more likely to have both Medicare and Medicaid (government-supported) insurance versus private insurance ($P = .03$). These patients were also more likely to have invasive lobular (versus ductal) histology ($P = .0001$). A small number of patients were BRCA positive (0.3%), all in the without LCIS group. Patients with LCIS were more likely to have undergone unilateral mastectomy versus lumpectomy ($P = .0008$). While the with LCIS cohort was less likely to have received adjuvant radiation ($P = .02$), there was no difference in adjuvant radiation for lumpectomy (breast conservation) patients specifically ($P = .50$). Follow-up was similar in patients with and without LCIS (mean 2.5 +/-1.6 years, range: 0–6.7 years versus 2.6 +/-1.6 years, range: 0–6.6 years; $P = 0.32$).

Patients with LCIS had a significantly increased future CBC risk (Table 2). Overall, CBC occurred in 3.3% of patients with LCIS and 1.0% of patients without LCIS ($P = .004$). This elevated risk was reflective of new invasive breast cancer. Patients with LCIS had an invasive CBC rate of 2.7% versus 0.7% in patients without LCIS ($P = .005$). There was no difference in future contralateral DCIS diagnosis ($P = 0.34$). For patients with LCIS, the relative risk of any CBC diagnosis was 3.3 (95% CI: 1.5,7.3, $P = .003$). The mean time from index BC diagnosis to new CBC was similar for invasive and in-situ disease ($2.84 \pm 1.55$ versus $2.86 \pm 1.84$ years, $P = .98$). In terms of CBC histology, patients with LCIS had equal rates of invasive ductal (n = 4) and invasive lobular (n = 4) cancers, whereas patients without LCIS had more invasive ductal (n = 8) than invasive lobular (n = 2) histology.

## Discussion

The purpose of this retrospective study was to define the rate of LCIS diagnosed concurrently with an invasive breast cancer, and to investigate the risk of contralateral breast cancer (CBC) in these patients during survivorship care. The results of this investigation show that patients with LCIS identified alongside an index invasive breast cancer have a significantly increased risk of future CBC. The prevalence of LCIS in invasive breast cancer surgical specimens was 16.6%, indicating a large subset of patients who may be at increased risk versus the average breast cancer survivor.

The general risk of CBC for all breast cancer patients is low, around 0.5% to 1% per year.[15] The patients without LCIS in our cohort fit into the standard risk range with a CBC rate of 1.0% in 2.6 years of follow-up. However, those with adjacent LCIS had a significantly higher CBC rate of 3.3% in the same timeframe. When diagnosed prior to BC, LCIS patients are recommended to consider increased screening (yearly screening mammogram plus yearly MRI or ultrasound) due to future breast cancer risk.[1,16,17] In contrast, breast cancer survivors are recommended to undergo annual screening mammogram rather than increased surveillance.[18] Our results call attention to the current guidelines because we have demonstrated that breast cancer survivors with LCIS alongside their invasive breast cancer have a future CBC risk which mirrors high-risk patients rather than typical BC survivors.[15] Thus it may be appropriate for women with LCIS diagnosed alongside an index breast cancer to consider on-going high-risk screening (yearly mammogram plus yearly MRI versus ultrasound) during the initial few years of survivorship care.

Given that most individuals with LCIS (96.7%) did not develop a CBC, we do not recommend changes to surgical management at the time of breast cancer diagnosis. Specifically, these data do not change the way we counsel patients concerning contralateral prophylactic mastectomy. Current guidelines

**Table 1.** Clinicopathologic factors.

| CHARACTERISTICS | INVASIVE BREAST CANCER WITHOUT LCIS, N = 1507 (%) | INVASIVE BREAST CANCER WITH LCIS, N = 301 (%) | *P*-VALUE* |
|---|---|---|---|
| Age (median, range) | 62 (56-68) | 64 (58-69) | .74 |
| Insurance | | | |
| Private | 698 (46.3) | 126 (41.9) | .03* |
| Medicare | 769 (51.0) | 165 (54.8) | |
| Medicaid | 18 (1.2) | 9 (3.0) | |
| Family history | | | |
| Breast cancer | 339 (22.5) | 76 (25.2) | .33 |
| Ovarian cancer | 49 (3.3) | 11 (3.7) | .72 |
| Personal history of LCIS | | | |
| Ipsilateral | 8 (0.5) | 4 (1.3) | .12 |
| Contralateral | 7 (0.5) | 3 (1.0) | .22 |
| Personal history of atypia | | | |
| Ipsilateral | 68 (4.5) | 16 (5.3) | .55 |
| Contralateral | 51 (3.4) | 7 (2.3) | .47 |
| BRCA1/2 positive<br>BC histologic type | 5 (0.3%) | 0 (0) | .59 |
| Invasive ductal | 1437 | 80 | .0001* |
| Invasive lobular | 70 | 221 | |
| BC Operation | | | |
| Lumpectomy | 1091 (72.3) | 188 (62.5) | .0008* |
| Unilateral mastectomy | 416 (27.7) | 113 (37.5) | |
| BC Treatment | | | |
| Adjuvant endocrine therapy | 1113 (73.9) | 237 (78.7) | .08 |
| Adjuvant radiation (all patients) | 1073 (71.2) | 195 (64.8) | .02* |
| Declined radiation (lumpectomy) | 103 (9.4) | 21 (11.2) | .50 |
| Average years of follow-up (mean, std, range) | 2.6 (1.6, 0-6.7) | 2.5 (1.6, 0-6.6) | .32 |

BC, breast cancer; LCIS, Lobular Carcinoma In-Situ.
*$P < 0.05$ statistically significant.

for the surgical management of breast cancer do not include the presence or absence of LCIS in surgical treatment decision-making, with both mastectomy and lumpectomy considered oncologically appropriate operations.[15] This is appropriate given the low rate of CBC documented here. While we note similarities in CBC risk between our cohort with LCIS and higher-risk patients in the short-term follow-up from our study, long-term data are needed to further definite the future breast cancer risk prior to making significant changes in surgical recommendations.

The question of secondary CBC risk for patients with LCIS has been addressed in limited prior publications. Mao et al[4] reviewed more than 10,000 individuals with a historic diagnosis of LCIS. They identified an increased risk of CBC, specifically for patients with hormone-positive LCIS. Their review included patients who were diagnosed at a time when LCIS was classified as cancer, thus hormone receptor status was assessed on a routine basis. With the modern reclassification of LCIS as a high-risk lesion (our cohort), hormone receptor status is no longer evaluated. As a result, the findings of Mao et al cannot be directly compared to our cohort but the trends in both studies are the same. The prior publication from Miller et al[14] is most similar to ours in terms of clinical question and patient cohorts. Their study of more

**Table 2.** Future contralateral breast cancer (CBC) risk in patients with and without LCIS alongside an index breast cancer (BC).

| | INVASIVE BREAST CANCER WITHOUT LCIS N = 1507 (%) | INVASIVE BREAST CANCER WITH LCIS N = 301 (%) | *P*-VALUE* | *RISK RATIO (95% CI)* |
|---|---|---|---|---|
| CBC: DCIS | 5 (0.3) | 2 (0.7) | .34 | |
| CBC: invasive BC | 10 (0.7) | 8 (2.7) | .005* | |
| CBC: All | 15 (1.0) | 10 (3.3) | .004* | |
| LCIS as a risk factor for CBC | | | .003* | 3.3 (1.5-7.3) |

CI, confidence interval; DCIS, ductal carcinoma in situ; LCIS, Lobular Carcinoma In-Situ.
*$P < 0.05$ statistically significant.

than 1800 patients with LCIS alongside DCIS identified an increased CBC risk in the group with LCIS, mirroring our results. The fact that our study along with results from Mao et al and Miller et al document increased CBC risk for patients with LCIS alongside their index BC is noteworthy and strengthens our conclusions.

With respect to study design, it is important to note that we purposefully elected not to collect data on cancer stage or receptor profiles. While stage and receptors are predictive of local regional recurrence (in the ipsilateral breast and axilla), metastatic recurrence, and disease-specific survival, they do not correlate to future CBC development, which was our primary outcome of interest.[19-21] In assessing clinicopathologic factors which differed between cohorts, two data points were identified. First, we identified a higher rate of invasive lobular carcinoma (ILC) versus invasive ductal carcinoma (IDC) in the with LCIS group. This result is not surprising as LCIS is more commonly associated with ILC than IDC.[5,6,9,22,23] However, women with ILC are not at a higher rate of CBC versus those with IDC, so this difference does not explain the higher rate of future CBC in those with LCIS.[20,24] The second factor which differed is that patients with LCIS had a higher rate of mastectomy than those without LCIS. We hypothesize this finding is reflective of more tissue available for pathologic evaluation, and thus a higher likelihood of identifying occult LCIS in the specimen but does not relate to future CBC. Given these factors which differed between cohorts do not influence CBC risk, separate statistical analysis controlling for these factors was not indicated.

There are limitations of this study that should be considered. Most importantly, the follow-up time (2.6 years) is relatively short-term in terms of survivorship care. Additional long-term CBC risk evaluation is warranted to determine if this difference persists. Our results should not be interpreted or extrapolated to a longer timeframe until more data are available. While our study included a larger number of patients (n = 1808), additional studies are warranted to verify our findings and investigate confounding variables. The prevalence of LCIS diagnosed with invasive breast cancer in our cohort is on the higher end of the range in prior publications.[9-14] Previous studies only included patients who underwent lumpectomy while we included patients who underwent lumpectomy and mastectomy, likely increasing the LCIS identification rate.

Despite these limitations, our study is important in that it adds significantly to a paucity of data evaluating future risk in patients with concurrent index breast cancer and LCIS. Future publications with long-term follow-up are warranted to better define the elevated risk demonstrated here and guide clinical management recommendations.

## Conclusions

Currently, LCIS is a clinically irrelevant finding if identified at the time of a patient's invasive breast cancer surgery. The results of this study challenge this assumption as patients with LCIS had a significantly increased future risk of contralateral breast cancer in the short-term survivorship timeline. Our results highlight a subset of patients with LCIS diagnosed alongside an index breast cancer (16%) who may benefit from closer clinical follow-up or increased high-risk screening during initial years of survivorship care, given this elevated risk.

## Author Contributions

M. C. B. and K. E. L. conceived the study design, data collection, interpretation and writing. A. L. A. and C. R. B. conceived the study design, data interpretation and editing. J. L. W. conceived the data interpretation and editing.

## ORCID iDs

Christa R Balanoff https://orcid.org/0000-0002-4320-122X
Kelsey E Larson https://orcid.org/0000-0003-1977-9459

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