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ORIGINAL PAPER

Trends in lobular carcinoma in situ management: endocrine therapy use in California and New Jersey

Schelomo Marmor[1] · Bonnie Jerome-D'Emilia[2] · James W. Begun[3] · Jane Yuet Ching Hui[1] · Ariella M. Altman[1] · Scott Kizy[1] · Todd M. Tuttle[1]

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Abstract

Purpose The diagnosis of lobular carcinoma in situ (LCIS) is a strong risk factor for breast cancer. Endocrine therapy (ET) for LCIS has been shown to decrease breast cancer risk substantially. The purpose of this study was to evaluate the trends of ET use for LCIS in two large geographic locations.

Patients and methods We identified women, ages 18 through 75, with a microscopic diagnosis of LCIS in California (CA) and New Jersey (NJ) from 2004 to 2014. We evaluated trends in unadjusted ET rates during the study period and used logistic regression to evaluate the relationship between patient, tumor, and treatment characteristics, and ET use.

Results We identified 3,129 patients in CA and 2,965 patients in NJ. The overall use of ET during the study period was 14%. For the combined sample, women in NJ were significantly less likely to utilize ET then their counterparts in CA (OR 0.77, CI 0.66–0.90, NJ vs. CA). In addition, patients in the later year period (OR 1.27, CI 1.01–1.59, 2012–2014 vs. 2004–2005) and women who received an excisional biopsy (OR 2.35, CI 1.74–3.17), were more likely to utilize ET. Uninsured women were less likely to receive ET (OR 0.61, CI 0.44–0.84, non-insured vs. insured status).

Conclusions We observed that an increasing proportion of women are using ET for LCIS management, but geographical differences exist. Health insurance status played an important role in the underutilization of ET. Further research is needed to assess patient outcomes given the variations in management of LCIS.

Keywords LCIS · Endocrine therapy (ET) · Geographic variation

Introduction

Lobular carcinoma in situ (LCIS) is a relatively rare finding, occurring in 0.5–4% of benign breast biopsies [1]. An increase in breast screening, and an increasing use of image-guided biopsy have likely lead to the increased incidence of LCIS noted in recent years [2], from 2.0 cases per 100,000 women (reported in the Surveillance Epidemiology, and End Results [SEER] database) in 2000 to 2.75 cases per 100,000 women in 2009 [1]. LCIS has been found to increase the absolute relative risk of invasive breast cancer in either breast eightfold [3]. While LCIS is considered a marker of increased risk rather than a precursor lesion [2], some studies have found that 18–20% of LCIS findings on core needle biopsy have been associated with an upgrade to ductal carcinoma in situ (DCIS) or invasive breast cancer on excisional biopsy [4].

There are several management strategies for LCIS, once current malignancy has been ruled out: surveillance, chemoprevention with endocrine therapy (ET), or prophylactic mastectomy [5]. Chuba et al., in a registry-based study of women diagnosed with LCIS who were treated with breast conservation surgery, found that 7% of the women went on to develop invasive breast cancer within 10 years, with equal distribution bilaterally [6]. Such findings have led to recommendations for chemoprevention for LCIS, rather than an emphasis on local control [7].

The National Comprehensive Cancer Network (NCCN) recommends surveillance for "classic" LCIS; however, the

✉ Schelomo Marmor
marm0014@umn.edu

[1] Department of Surgery, University of Minnesota, Minneapolis, MN, USA

[2] Rutgers University School of Nursing - Camden, Camden, NJ, USA

[3] Department of Health Policy and Management, University of Minnesota, Minneapolis, MN, USA

guidelines conclude that it is reasonable to consider further surgery for histologically aggressive subtypes such as pleomorphic LCIS [4]. Although LCIS is known to increase a woman's risk for breast cancer over time, chemoprevention has been found to be effective in decreasing that risk. A large randomized clinical trial, the National Surgical Adjuvant Breast and Bowel Project [NSABP] P-1 Trial, evaluated the effectiveness of chemoprevention in both pre- and postmenopausal women [8]; the number of subsequent invasive and non-invasive breast cancers was reduced by approximately 50% with a 5-year course of tamoxifen as compared to placebo [8]. The P-1 Study found a 43% decrease in breast cancer risk after 7 years of follow-up, [8] and so the NCCN Breast Cancer Risk Reduction Panel recommends the consideration of tamoxifen for healthy pre- and postmenopausal women over the age of 35 who have a history of LCIS [4]. Tamoxifen or raloxifene is recommended for postmenopausal women following a diagnosis of LCIS [4]. The American Society of Clinical Oncology (ASCO) updated its clinical practice guidelines for breast cancer risk reduction in 2013 to state that ET should be discussed as an option with women who have been diagnosed with LCIS [9]. The use of chemoprevention as a method of risk reduction for women with LCIS has, however, been consistently underutilized [9–11].

Given the increase in the finding of LCIS in women who have not otherwise been diagnosed with breast cancer, the need to clarify and to codify management recommendations has become critical. The purpose of this study was to evaluate recent trends of ET utilization in the management of LCIS in the United States by conducting a population-based study among patients diagnosed with LCIS using the California Cancer Registry (CCR) and the New Jersey State Cancer Registry (NJSCR). We analyzed recent trends in the use of ET for LCIS and identified how these patterns vary across patient characteristics as well as these two large geographic regions.

Methods

Data

We used data from 2004 to 2014 from two independent data sources, the CCR and the NJSCR, to identify women with LCIS (defined by the SEER ICD-03 histology code 8520). Cases are reported to the Cancer Surveillance Section of the California Department of Public Health from hospitals and any other facilities providing care or therapy to cancer patients residing in California (CA). The NJSCR is a population-based registry, mandated by state law that collects data on all cancer cases and specific precancerous diseases diagnosed and/or treated in New Jersey (NJ) since 1 October 1978. Although both registries adhere to national data collection methods, there are some discrepancies in ET variable collection between the two registries. In CA, the data are extracted from medical records. Records from each facility where the patient was treated are consolidated for this variable. Information is collected from the time of diagnosis until first course of therapy ends. First course ends when the treatment is completed or when there is documentation of disease progression, recurrence, or treatment failure. If there is no documentation, first course ends one year after the date of diagnosis. In NJ, although patient records are extensively validated and verified by the registry, there is a lack of access to treatment records from physician offices or other non-hospital facilities that might administer or prescribe the hormone therapy. Data on these cases must be reported to the NJSCR within 6 months of diagnosis, and all providers who diagnose cancer in the state must report cases to the registry [12] The NJSCR has participated in the Centers for Disease Control and Prevention's National Program of Cancer Registries since its inception, is included in the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) expansion registry, and has been awarded the Gold Standard for data quality by the North American Association of Central Cancer Registries [13, 14].

CCR and NJSCR collect patient, tumor, and treatment characteristics, including age at diagnosis, race, payer information (insurance status), primary tumor site, tumor histologic subtype, tumor stage, and ET utilization. Our study was approved by the University of Minnesota and Rutgers University Institutional Review Boards.

Patients

We limited our study to women with a microscopic diagnosis of LCIS. We excluded men, women diagnosed before 18 or after 75 years of age, those diagnosed by death certificate or autopsy, women whose cancer was reported by a nursing home, those with simultaneous occurrence of invasive breast cancer or DCIS, those without microscopic confirmation of LCIS, and those diagnosed outside of CA and NJ. We also excluded women who received unilateral and bilateral mastectomy as treatment for LCIS.

Statistical analysis

We evaluated the unadjusted differences between demographic and treatment characteristics among patients in the two cohorts. We compared unadjusted ET rates during the study period using the Cochran Armitage test for trend. We then used a logistic regression model to evaluate the relationship between patient, tumor, and treatment characteristics, and the receipt of ET. All models included the year of diagnosis, patient age, insurance status [insured (private,

Medicare, Medicaid), non-insured], race (non-Hispanic white, black, other), surgery type (none, excisional biopsy). We confirmed that all patterns we observed persisted when we combined the data from the two separate registries over the entire study period. All statistical analyses were completed using SAS software, version 9.3 (SAS Institute, Cary, NC). Results were identified as statistically significant only at a $p \leq 0.05$ corresponding to a 95% confidence interval (CI).

Results

Patient population

We identified a total of 3,129 patients in CA and 2,965 patients in NJ who were diagnosed with LCIS (Table 1). The overall use of ET during the study period was 14% in the LCIS group. This compared to an overall use of 36% ($n = 66{,}422$) in NJ and 35% ($n = 382{,}774$) in CA among invasive lobular carcinoma patients. The majority of patients in both LCIS groups were non-Hispanic white (63% CA; 73% NJ), were over the age of 45 years (83% CA; 86% NJ), and underwent excisional biopsy (88% CA; 86% NJ). Although we found an increasing proportion of ET use over time in both CA (11% in 2004 to 20% in 2014) and NJ (12% in 2004 to 15% in 2014), the unadjusted trends were not statistically significant (Fig. 1a and 1b). We observed an increasing proportion of ET use by age (Fig. 2a and b) in CA (12% for ages 18–44 vs. 17% for ages 65–74). This age trend was not evident in NJ (10% for ages 18–44 vs. 8% for ages 65–74 and 5% for ages 75–85).

Factors associated with endocrine therapy use in California and New Jersey

In the logistic regression analysis for CA alone, we found that older women [odds ratio (OR) 1.49, CI 1.04–2.12, ages 55–64 vs. ages 18–44; and OR 1.71, CI 1.16–2.53, ages 65–74 vs. ages 18–44] were more likely to receive ET for

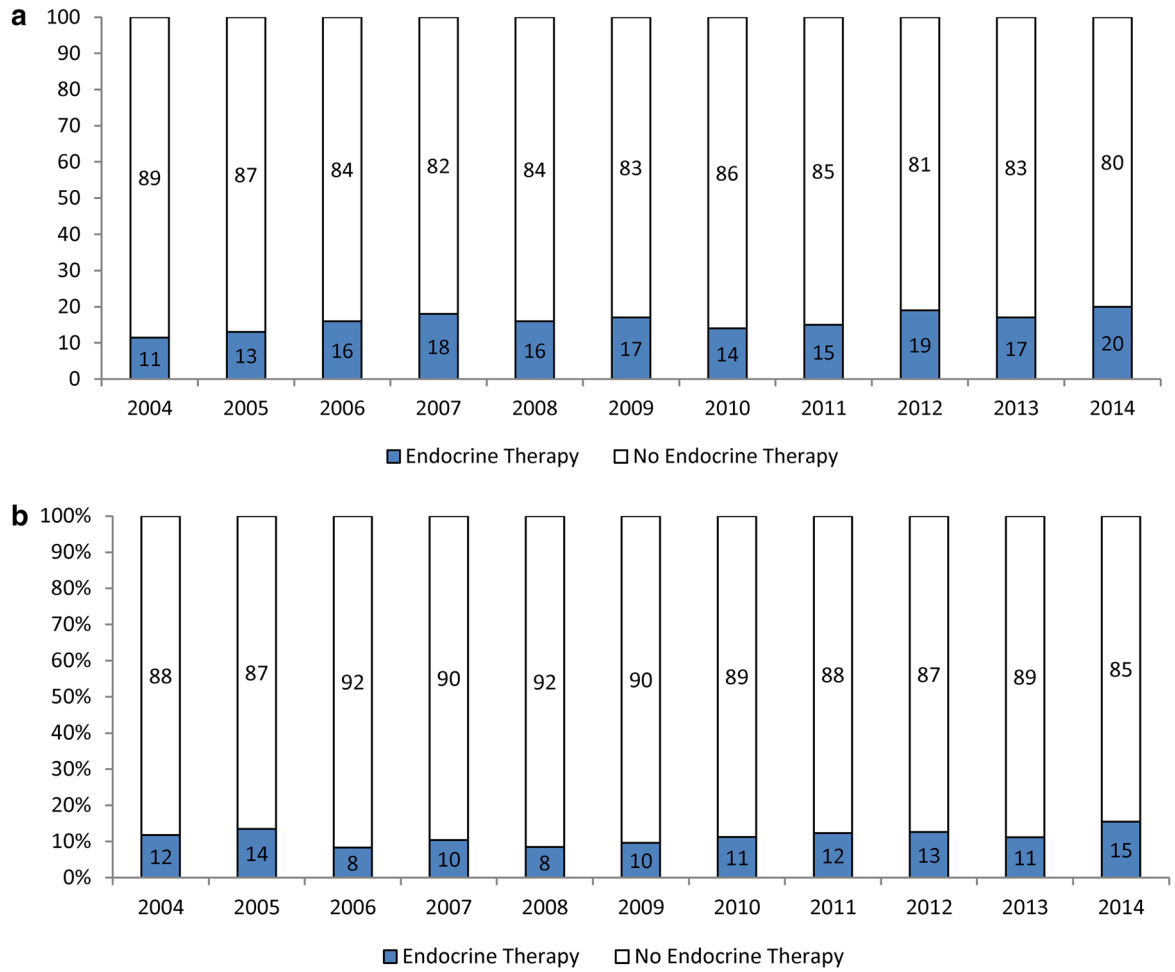

Fig. 1 **a** Endocrine therapy use in California over time. **b** Endocrine therapy use in New Jersey over time

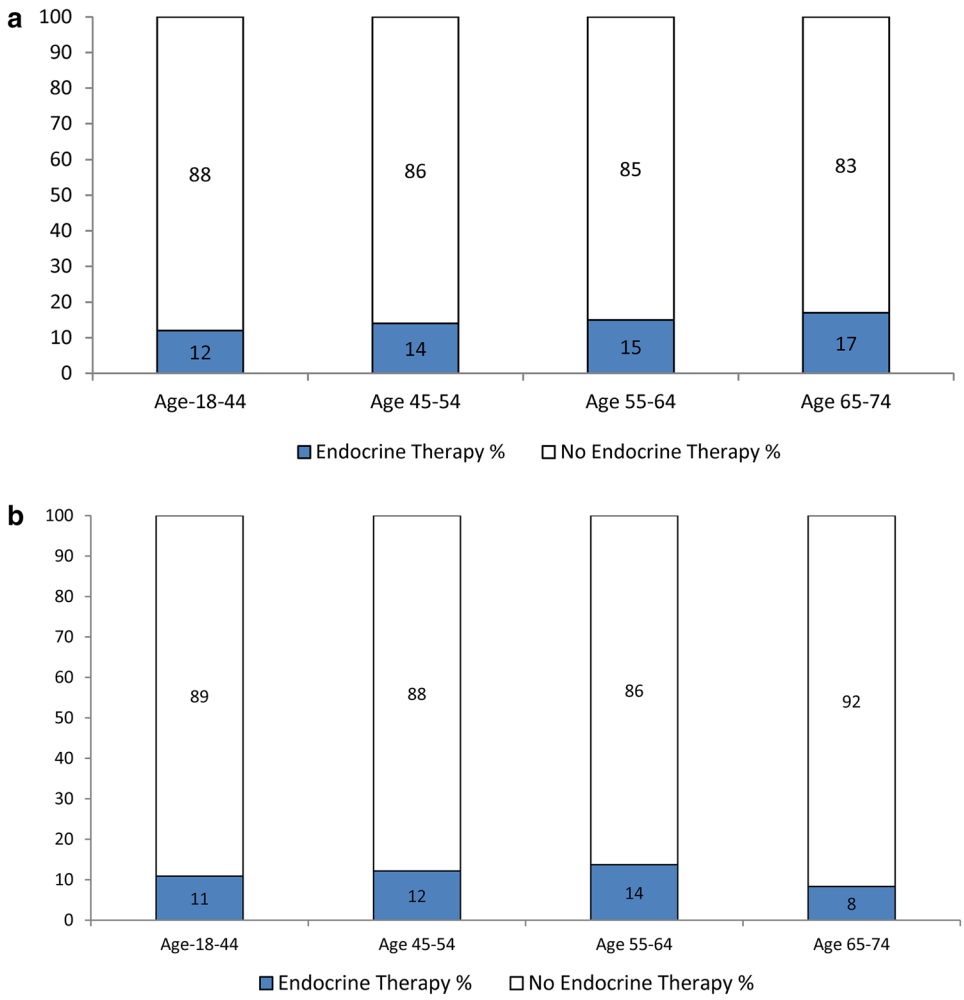

Fig. 2 **a** Endocrine therapy use in California by age. **b** Endocrine therapy use in New Jersey by age

the management of LCIS, when adjusted for patient and treatment characteristics. Other factors that were significantly associated with an increased likelihood of ET use in CA included excisional biopsy (OR 1.75, CI 1.17–2.64, excisional biopsy vs. none) and later years (OR 1.44, CI 1.03–2.01, 2012–2014 vs. 2004–2005). In NJ, the only significant factor associated with ET utilization was the receipt of excisional biopsy (OR 3.91, CI 2.29–6.68, excisional biopsy vs. none).

Factors associated with endocrine therapy use in combined sample

We observed considerable geographic variation in ET use between CA and NJ. When we combined the data from the two states, we found that women in NJ were significantly less likely to utilize ET for LCIS than their counterparts in CA (OR 0.77, CI 0.66–0.90, NJ vs. CA) (Table 2). Women with a later year of diagnosis (OR 1.27, CI 1.01–1.59, 2012–2014 vs. 2004–2005) and women who received an excisional biopsy (OR 2.35, CI 1.74–3.17, excisional biopsy vs. no surgery) were more likely to utilize ET. We also found that the 55–64-year age group was significantly more likely to utilize ET over the 11-year period (OR 1.33, CI 1.04–1.70, age 55–64 vs. age 18–44). Additionally we observed that uninsured women were less likely to receive ET (OR 0.61, CI 0.44–0.84, uninsured vs. insured status).

Discussion

This study examined the variations in the use of ET as a management strategy for LCIS in two large states: NJ and CA. Our results illustrate that the use of ET for LCIS indeed varies widely. Overall, we found that women in CA were more likely to use ET for LCIS, and older women were more likely to use ET than their younger counterparts during this 11-year period, after adjusting for other factors. This age trend was particularly prominent in CA. We also found that health insurance played an important role in the underutilization of ET.

Table 1 Basic characteristics of lobular carcinoma in situ, New Jersey and California 2004–2014

	New Jersey ($n=2,965$)		California ($n=3,129$)	
	n	%	n	%
Diagnosis year				
2004	246	8	254	8
2005	218	7	283	9
2006	251	8	271	9
2007	251	8	291	9
2008	280	9	290	9
2009	280	9	354	11
2010	276	9	268	9
2011	281	9	244	8
2012	293	10	274	9
2013	268	9	291	9
2014	321	11	309	10
Age				
18–44	422	14	543	17
45–54	1,598	54	1,444	46
55–64	621	21	726	23
65–74	324	11	416	13
Race				
Non-Hispanic White	2,175	73	1,984	63
Black	226	8	170	5
Other	564	19	975	31
Insurance status				
Private	2,174	73	2,512	80
Medicare	315	11	309	10
Medicaid	62	2	153	5
No insurance	414	14	155	5
Surgery type				
None	412	14	361	12
Partial mastectomy	2,553	86	2,768	88
Endocrine therapy				
No	2,257	76	2,551	82
Yes	352	12	489	16
Unknown	356	12	89	3

Table 2 Factors associated with endocrine therapy utilization in New Jersey and California (combined) 2004–2014

	Odds ratio	95% confidence limits	
Year of diagnosis			
2004–2005	REF		
2006–2007	1.19	0.92	1.53
2008–2009	0.99	0.77	1.27
2010–2011	0.93	0.71	1.21
2012–2014	**1.27**	**1.01**	**1.59**
Age			
18–44	REF		
45–54	1.20	0.96	1.50
55–64	**1.33**	**1.04**	**1.70**
65–74	1.21	0.91	1.61
Race			
Non-Hispanic White	REF		
Non-Hispanic Black	0.98	0.72	1.33
Other	1.11	0.93	1.32
Insurance status			
Insured (private, medicare, medicaid)	REF		
No insurance	**0.61**	**0.44**	**0.84**
Surgery			
None	REF		
Partial mastectomy	**2.35**	**1.74**	**3.17**
Geography			
California	REF		
New Jersey	**0.77**	**0.66**	**0.90**

Bold denotes statistical significance of $p \leq 0.05$

Insurance status has been associated with breast cancer across the continuum of care. Lack of insurance has been associated with a lower rate of screening, [14] later stage at diagnosis, [13] disparities in treatment, [14] and poorer patient outcome [15]. Because there are few studies of ET use in LCIS, we examined the literature on ET use for chemoprevention in high-risk women (excluding studies of BRCA positive women). Smith et al. conducted a meta-analysis of studies that addressed the uptake and adherence to ET for breast cancer chemoprevention in high-risk women [16]. Of the 57 articles reviewed, only two studies considered insurance status, but did not find it to be significant [17, 18]. More recent studies have not considered insurance status, focusing primarily on patient and physician-related barriers rather than socioeconomics [19–21]. One factor that is often related to insurance status is receipt of a physician recommendation. Women who lack insurance (either private or public) often also lack a usual source of care, which then may impede their access to preventive care [22, 23].

Although the effectiveness of ET for LCIS has been documented, [8, 24] the actual trends in ET utilization have not been reported. We found the use of ET increasing over time in CA and NJ; however, the time trend we observed was not significant or consistent. Despite consistent findings from large clinical trials and recommendations from ASCO, NCCN, and the US Preventive Services Task Force (USPSTF), population-based estimates of ET use have remained low (14% in our study) [9]. Bambhroliya et al. suggest that this continued low use may be related to the fact that most of the ET eligible high-risk women are in fact being managed in the primary care setting, and that primary care providers (PCP) may lack the disease-specific knowledge that would be needed to identify women who would be best served by

ET [9]. Using the modified Gail model of risk estimation, Brewster et al. found that in the community setting, a PCP would have to screen 26 women aged 40–49 and 142 women aged 60–70 to find one woman who would be appropriate for treatment with tamoxifen [25]. Studies have found that very few PCPs are comfortable using Gail risk scores to identify women at high-risk for breast cancer. The most commonly cited barriers against its use were lack of time and familiarity [9].

In both states, ET use was associated with surgical treatment (excisional biopsy). Ward et al. (in a large registry-based study) found that breast conservation surgery was the most common surgical management across all age ranges of women (in 80% of women diagnosed with LCIS), although choice of surgical management was related to age, with younger women more likely to undergo unilateral or bilateral mastectomy [7]. In CA, age was a relevant factor in the use of ET, and in the combined sample, patient age (55–64) was related to ET use. Age has not been found to be a predictor of ET use in studies of chemoprevention. Using a meta-analysis, Smith et al. reported that age was either not associated or inconsistently associated with use of ET [16]. Although tamoxifen has been found to be safe in premenopausal women, as has raloxifene in postmenopausal women, utilization remains low in this population [26–28]. Studies that have examined the low use of tamoxifen for both pre- and postmenopausal women and raloxifene for postmenopausal women have found that physicians may choose not to recommend these medications due to concern about side effects, and that women who know more about the risks and benefits of ET may be less likely to opt for the treatment [29]. Comparing National Health Interview Survey data from 2000 to 2010, Waters et al. found that there appeared to be a slight shift from tamoxifen to raloxifene, with no overall increase in ET use [29]. This finding would be consistent with the use of ET in postmenopausal women, which likely is reflected in the CA data. Although tamoxifen does not directly cause early menopause, it is also possible that the inconsistently increasing use of ET over time that we observed is a reflection of the ambivalence of younger women to use ET (in that the side effects of the treatment are similar to those of menopause), with the concomitant increase in younger women choosing mastectomy or bilateral mastectomy as a response to a diagnosis of LCIS [7]. Studies have found that younger women are more likely to discontinue use of ET [30]. These findings are probably related to the desire of younger women to avoid side effects and the lack of a compelling physician recommendation [20, 29, 31]. Bober et al. found that although all women in a small study (129 subjects) were counseled by physicians about the risks and benefits of ET, a subset of women did not consider that counseling to constitute a physician recommendation [31]. Other studies have found that the receipt of ET is relatively low in the group of women most likely to benefit from its use and also observed significant variation exists with respect to patient, tumor, site, and treatment factors [32, 33].

Our study has several registry-related limitations. Detailed patient and tumor information that may have influenced treatment decisions was not available from the cancer registry databases. The CA and NJ registries do not distinguish between different variants of LCIS (i.e., pleomorphic LCIS vs. non-pleomorphic), nor do they specify which drug has been ordered for chemoprevention. Important information regarding family history, genetic testing results, mammographic, or MRI findings was not available from these databases, but these breast cancer risk factors may influence a patients' decision regarding risk-reduction strategy. Although both registries adhere to national data collection methods, there are some discrepancies in ET variable collection between the two registries that could potentially introduce some bias into our study. For example, it is possible that the registrars at hospitals in CA have more access to "unified" medical records and can therefore track hormone treatment among their breast cancer patients better than NJ and that could explain some of the "unknowns" in the NJ data. In CA, the data are extracted from medical records. Records from each facility where the patient was treated are consolidated for this variable. Information is collected from the time of diagnosis until first course of therapy ends. First course ends when the treatment is completed or when there is documentation of disease progression, recurrence, or treatment failure. If there is no documentation, the first course ends 1 year after the date of diagnosis. In NJ, although patient records are extensively validated and verified by the registry, there is a lack of access to treatment records from physician offices or other non-hospital facilities that might administer or prescribe the hormone therapy; it is possible that for some women in the "unknown" category (Table 1), the endocrine treatment was ordered after the data were collected, and that would introduce some error within the 12% "unknown" category that we identified. However, we believe that our results are robust and that the observed geographic trends would not dramatically change due to data collection discrepancies within the unknown category.

Despite these limitations, our study provides the largest overview to date of the ET utilization patterns and trends for patients with LCIS in the United States. Our results demonstrate that a relatively increasing proportion of women are using ET for LCIS management and that geographical differences exist in the US. Consistent with previous studies, insurance status was a factor in the receipt of ET. Other studies have shown that hospital and surgeon characteristics have been associated with the quality of care that women receive for breast cancer treatment [31–34]. Further research is necessary to identify the practice patterns and other contributing factors that are associated with variations in ET utilization

and the most effective methods of educating physicians and high-risk women about the benefits of chemoprevention in the reduction of breast cancer risk over time.

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Compliance with ethical standards

Conflict of interest The authors of this manuscript have no conflicts of interest to disclose.

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