Lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH) are relatively uncommon breast lesions, which are typically discovered in breast biopsies taken for other reasons. The first description of LCIS was reported by Ewing in 1919, who depicted this lesion as an “atypical proliferation of acinar cells” of the breast (1). The main characteristics of this lesion, however, were not thoroughly documented until 1941 in the seminal study by Foote and Stewart, in which the term LCIS was coined to refer to a spectrum of “noninfiltrative lesions of a definitely cancerous cytology” that would constitute precursors of invasive breast cancer, and be composed of a monomorphic population of dysplastic cells that expand the terminal duct–lobular units (2). A less-prominent in situ proliferation composed of cells cytologically identical to those of LCIS, and associated with a lower risk of breast cancer development, was subsequently identified and named ALH (3). In a review of 211 cases of LCIS not associated with other forms of breast cancer, Haagensen et al. (4) observed the difficulties in differentiating between LCIS and ALH, and suggested that the term LCIS not associated with invasive cancer would constitute a misnomer, given that the available evidence at that time supported the contention that these lesions would in fact constitute a “benign, non-infiltrating, special microscopic form of lobular proliferation of the mammary epithelium” (4). The term lobular neoplasia (LN) was subsequently put forward to refer to the entire spectrum of these in situ lesions, including ALH and LCIS (4). Although surgeons, oncologists, and pathologists are familiar with the concept of LCIS, the terminology and classification for these lesions, their biological significance (risk indicator vs. precursor for invasive cancer), and the best course of management following diagnosis remain controversial. This chapter will discuss the clinicopathological and molecular characteristics of LN, and the impact of recent developments on the management of these lesions.

Several of the concepts initially put forth by Foote and Stewart (2) on the biology of LCIS remain valid today. The term LCIS was chosen to emphasize the histologic similarities between the cells of LCIS and those of frankly invasive lobular carcinoma (ILC), and, importantly, was not meant to infer that the cell of origin resided in the lobules; in fact, it was acknowledged that LCIS would originate in the terminal duct–lobular unit and small ducts (2). In addition, LCIS was reportedly to be frequently multicentric and bilateral, and not readily identifiable on gross examination. Microscopically, the cells that constitute LCIS were thought to disseminate through the ductal system in a way akin to that of Paget’s disease; however, LCIS was almost never seen in association with true Paget’s disease of the nipple (2). Based on the frequent identification of LCIS in association with ILC and following the analogy of ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC), Foote and Stewart (2) hypothesized that the neoplastic cells of LCIS would still be contained within a basement membrane, and that this lesion would constitute a “hazard” (i.e., risk factor) of breast cancer development and a step along the pathway to the development of invasive cancer. Hence, based on the evidence available, simple mastectomy was suggested as the standard form of treatment (2).

Emerging data throughout the 1970s from Haagensen et al. (4) and others (5) demonstrating that the risk of breast cancer development following a diagnosis of LCIS was lower than expected for a direct precursor lesion (approximately 1% per year) and was conferred equally to both breasts generated controversy regarding the significance of these lesions and led to disparate recommendations for management, ranging from observation only to bilateral mastectomy. In current practice, a diagnosis of ALH or LCIS is typically perceived as a risk indicator rather than a precursor of subsequent carcinoma and, as such, radical treatment has fallen out of favor. Yet, observational evidence to suggest that the
risk of breast cancer development following a diagnosis of LN is higher in the ipsilateral than in the contralateral breast and compelling molecular data that demonstrate that ALH and LCIS are clonal neoplastic proliferations that commonly harbor the same genetic aberrations as those found in adjacent invasive cancers (6–10) have reinstated the notion that ALH and LCIS are both non-obligate precursors and risk indicators of invasive breast cancer. Questions regarding the biology and optimal management of these lesions have returned to the forefront of breast cancer research and practice.

**EPIDEMIOLOGY AND CLINICAL FEATURES**

LCIS is most frequently diagnosed in women aged 40 to 55 years (4,11). The true prevalence of LCIS in the general population, however, is difficult to estimate and likely exceeds the incidence, given that it does not present as a mass lesion nor does it have a specific radiographic appearance. Lesions diagnosed in the pre-mammography screening era were typically incidental microscopic findings in biopsies and excision specimens obtained for other reasons (2,4). The reported incidence of LCIS in otherwise benign breast biopsy specimens ranges from 0.5% to 3.8% (4,11), whereas population-based data reported to Surveillance, Epidemiology, and End Results (SEER) from 1978 to 1998 demonstrate an incidence of 3.19 per 100,000 women (12). It is noteworthy, however, that during this time period there was an observed four-fold increase in the number of LCIS cases reported among women over 40 years of age, with the highest incidence rate (11.47 per 100,000 person-years) in 1998 among women 50 to 59 years of age. While this trend may reflect the increasing use of mammography and image-guided biopsies during this time period (12,13), the impact of other factors, such as the use of postmenopausal hormone replacement and more accurate pathologic diagnosis of LN based on ancillary immunohistochemical markers (see below) remains a matter of speculation. LCIS is often multifocal, with more than 50% of patients diagnosed with LCIS showing multiple foci in the ipsilateral breast. Furthermore, bilateral lesions are reported in approximately one-third of patients (14,15). Such multifocality in a clinically non-detachable lesion is one of the reasons why planning subsequent management has proven problematic and contentious. More recent imaging series suggest that LCIS may be associated with microcalcifications (16), and LCIS has been reported to enhance on MRI (17); however, imaging criteria to differentiate LCIS from overt malignancy are lacking, and, as such, women with LCIS are frequently subject to multiple biopsies demonstrating otherwise benign findings.

The clinical characteristics of LCIS, including its multifocal and bilateral distribution, and evidence of familial clustering (18,19) have led to the hypothesis that these lesions could be underpinned by germline genetic abnormalities. Although a hereditary form of diffuse gastric cancer and breast lobular carcinoma caused by *CDH1* germline mutations (20) has been described, the potential genes involved and the pattern of inheritance of familial LCIS outside of this context remain unclear (see below). The clinical characteristics of LCIS that support its role as a risk factor for the subsequent development of breast cancer include the cumulative long-term risk of breast cancer development that is generally conferred to both breasts, averaging 1% to 2% per year, and the observation that not all breast cancers developing after a diagnosis of LCIS are of lobular histology (reviewed in reference (21)). The incidence of invasive breast cancer following a diagnosis of LCIS is steady over time (22), with a similar number of invasive lesions being reported within and after 5 years of follow-up (23). Others have also demonstrated the cumulative long-term risk, with one study reporting that over 50% of patients developed breast cancer between 15 and 30 years of follow-up (5). ALH is also associated with an increased risk of subsequent breast cancer; however, this is of a lower magnitude than that conferred by LCIS. Patients diagnosed with ALH have a four- to five-fold higher risk than the general population (i.e., women of comparable age who have had a breast biopsy performed with no atypical proliferative disease diagnosed), whereas a relative risk of 8 to 10 times is conferred by a diagnosis of LCIS (11,24,25). Hence, these observations suggest that the term LN, albeit helpful to describe this group of lesions collectively, may not suffice to guide the management of patients with lobular lesions, and specific classification of LN into ALH and LCIS may still be justified. It should be noted, however, that the distinctions between ALH and LCIS are subjective and, for some experts, the differences between these two categories of LN are more easily expressed in words than in actual practice (23).

The risk of breast cancer development following a diagnosis of ALH or LCIS is bilateral (14,22,26), which is consistent with the notion that these lesions are risk indicators; however, some have reported a higher rate of breast cancer in the ipsilateral breast (9,21,27), supporting a precursor role for LCIS. The histological type of breast cancer following a diagnosis of LN also differs among these reports. In studies that suggest the risk is conferred equally to both breasts, there are, similarly, an equal number of subsequent IDCs and ILCs reported to occur after a diagnosis of LCIS (22), which is consistent with the notion that LCIS would not constitute a true precursor lesion. On the other hand, in most studies that report a higher incidence of ipsilateral cancer development, the majority of the cancers are of lobular histology (8,21,23). This clinical observation, in parallel with SEER data demonstrating an increasing incidence of both LCIS and ILC from the late-1980s to the mid-1990s among women 50 years of age and older (12,28), have led to renewed interest the debate over the clinical significance of LCIS. Taken together, the current epidemiological, observational, and clinical data support the contention that LN is not only a risk indicator, but also a non-obligate precursor of invasive breast cancer. This notion is lent further credence by the striking morphologic similarities between cells of ALH or LCIS and ILC, and molecular data demonstrating the clonality between LN and synchronous invasive breast cancer (see below); in particular, the presence of concordant gene copy number and allelic abnormalities (6,29), mitochondrial DNA mutations (7), and identical *CDH1* gene mutations in matched LCIS and ILC from the same patients (10).

**HISTOLOGICAL FEATURES AND CLASSIFICATION**

Despite the controversies surrounding the clinical implications of ALH and LCIS, their histologic features have been well characterized. The latest World Health Organization (WHO) classification of breast tumors defines LN as “a spectrum of atypical epithelial lesions originating in the terminal duct lobular unit and characterized by a proliferation of generally small, non-cohesive cells, with or without pagetoid involvement of the terminal ducts” (30). At scanning magnification, these lesions are characterized by a variable enlargement of the acini, which are filled up and, at least in part, are expanded by a proliferation of monomorphic population of dyshesive
Arguably, a more relevant distinction is between the classic form of LN and the pleomorphic variant of LCIS (PLCIS), which was first identified as a distinct entity by Eusebi et al. in 1992 (34). This variant is characterized by pleomorphic cells that are substantially bigger than those of classic LN (31,34), and by more abundant, pink, and often finely granular cytoplasm. Features of apocrine differentiation are frequently found (34,35). As compared to the nuclei of classic LN, PLCIS nuclei are bigger (four times the size of lymphocyte nucleus), more pleomorphic, and atypical nuclei, often containing conspicuous nucleoli (Fig. 22-5). PLCIS not uncommonly presents with central, comedo-type necrosis and microcalcifications; yet, necrosis is not required for the diagnosis. Recognition of the pleomorphic subtype is important because the combination of cellular features, necrosis, and calcification can lead to difficulty in differentiation from DCIS, and potentially overtreatment, although data regarding the natural history of PLCIS are very limited. Until additional data regarding the natural history of PLCIS are available, this distinction has important implications for treatment. Whereas some advocate for a more aggressive approach to PLCIS, with treatment recommendation akin to those for DCIS, it should be noted that this approach is supported...
only by molecular data demonstrating that PLCIS shares many similarities with pleomorphic ILC, not by long-term outcomes data.

Additional variants of LN have been reported, including apocrine, histiocytoid, rhabdoid, endocrine, amphicrine, and the apocrine PLCIS variant (21,30). The biological and clinical significance of these lesions also remains to be determined.

A further system for classification of LN has been proposed using the terminology lobular intraepithelial neoplasia (LIN), with subdivision, based on morphologic criteria and clinical outcome, into three grades (LIN 1, LIN 2, LIN 3), with LIN 3 representing the PLCIS end of the spectrum (36,37). This system pre-supposes that the risk of invasive carcinoma development would be related to increasing grade of LIN. This classification system, albeit interesting and potentially sparing women from a diagnosis of “carcinoma” in the case of LCIS, is supported by limited evidence and has not been endorsed in the latest edition of the WHO classification (30).

### TABLE 22-1

**Cytological and Histopathological Features of Classic and Pleomorphic Lobular Carcinomas**

<table>
<thead>
<tr>
<th>Type of Carcinoma</th>
<th>Nuclear Size&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Nuclear Pleomorphism&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Nucleoli</th>
<th>Cytoplasm</th>
<th>Dyshesion</th>
<th>Central Necrosis</th>
<th>Calcifications</th>
<th>Apocrine Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCIS Type A</td>
<td>1.5x</td>
<td>1, rarely 2</td>
<td>Inconspicuous</td>
<td>Scant</td>
<td>Present, but inconspicuous</td>
<td>Absent</td>
<td>Occasional</td>
<td>Absent</td>
</tr>
<tr>
<td>LCIS Type B</td>
<td>2x</td>
<td>1 or 2</td>
<td>Inconspicuous to small</td>
<td>Moderate</td>
<td>Yes</td>
<td>Absent</td>
<td>Occasional</td>
<td>Absent</td>
</tr>
<tr>
<td>PLCIS</td>
<td>≥4</td>
<td>Usually 3</td>
<td>Present, often small</td>
<td>Moderate to abundant</td>
<td>Yes</td>
<td>Frequent</td>
<td>Frequent</td>
<td>Focal</td>
</tr>
<tr>
<td>Apocrine PLCIS</td>
<td>≥4</td>
<td>3</td>
<td>Present, prominent</td>
<td>Abundant</td>
<td>Yes</td>
<td>Frequent</td>
<td>Frequent</td>
<td>Defining feature</td>
</tr>
</tbody>
</table>

<sup>a</sup>Nuclear size in comparison with the size of a lymphocyte.

<sup>b</sup>Using the nuclear pleomorphism scheme for DCIS.

LCIS, lobular carcinoma in situ; PLCIS, pleomorphic LCIS.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of LN includes artifacts, benign breast lesions, and other forms of breast cancer precursors. Prolonged periods of warm ischemia and poor tissue fixation, not uncommonly seen in mastectomy specimens, can result in an artifactual discohesion of cells within a lobular unit, which can mimic ALH and LCIS (21). Benign lesions that may superficially resemble LN include foci of lactational change, where the cells harbor intracytoplasmic lipid droplets, and clear-cell metaplasia (21). More troublesome is the histologic appearance of LN colonizing other benign breast lesions, including fibroadenoma, sclerosing adenosis, and radial scar, which, clinically and radiologically, can present as a mass. Particularly well-known but rather remarkably problematic examples of LN in sclerosing adenosis may resemble IDC to the unwary, due to the distorted appearance of the residual ductal and lobular structures lined by LN cells and immersed in a sclerotic stroma (21,30). In this context, immunohistochemical markers to demonstrate the presence

FIGURE 22-3  Pagetoid spread. Lobular carcinoma in situ cells (arrowheads) are seen growing beneath, and displacing inward, the luminal epithelium of a duct.

FIGURE 22-4  Atypical lobular hyperplasia. A lobular unit is focally and partially filled by characteristic cells with intracytoplasmic lumina (arrowheads).
CHAPTER 22 | LOBULAR CARCINOMA IN SITU: BIOLOGY AND MANAGEMENT

The advent of laser capture microdissection and high-throughput genomic and transcriptomic methods have allowed for the study of pre-invasive lesions of the breast. In the last decade, molecular genetic studies have provided a wealth of increasingly more coherent data on the pathways of breast cancer evolution and how these findings correlate with morphological features (8,30). It is currently accepted that ER-positive and ER-negative breast cancers are fundamentally different diseases, with distinct patterns of gene expression changes (41) and repertoires of genetic aberrations (42).

ER-positive breast cancers are characterized by recurrent deletions of 16q, gains of 1q and 16p; additional genetic aberrations including CCND1 and FGFRI amplification, gain of 8q, and losses of 11q, 13q, and 17q are observed in high-grade lesions. ER-negative breast cancers, on the other hand, are characterized by a more complex pattern of gene copy number aberrations, with multiple low-level gains and deletions affecting multiple chromosomal arms; deletions of 16q, however, are remarkably rare in these cancers (8,30). The repertoires of mutations in ER-positive and ER-negative disease are also different. For instance, while ER-positive cancers are characterized by recurrent PIK3CA, PTEN, AKT1, GATA3, CDH1, MAP3K1, MAP2K4, and CDKNIB mutations, ER-negative cancers often harbor TP53 mutations (42).

Molecular studies of LN have been instrumental in highlighting the role of E-cadherin inactivation in the development of lobular lesions and in providing evidence to demonstrate that ALH and LCIS are in fact non-obligate precursors of invasive cancer rather than being simply risk indicators of subsequent breast cancer development.

**Immunophenotype**

All subtypes of LCIS are associated with strong expression of ER-alpha (ERα), ER-beta (ERβ), and PR in the majority of neoplastic cells (Table 22-2). Classic forms of LN usually display an immunohistochemical profile consistent with that of ER-positive breast cancer with a less-aggressive clinical behavior (i.e., luminal A), including lack of HER2 and p53 expression, and exhibit low proliferation indices, as defined by Ki67. PLCIS, on the other hand, may express to a higher level of ER and PR expression, and frequently harbors HER2 gene amplification and positivity, and its Ki67 labeling indices are usually higher than those of classic LCIS. These features, however, are reported to be predominantly found in the apocrine subtype of PLCIS which also often express GCDFP-15 (gross cystic disease fluid protein-15), a marker of apocrine differentiation (21,30,35); however, the criteria to differentiate between PLCIS and apocrine PLCIS remain a matter of controversy.

Although the high molecular weight cytokeratins identified by the clone 34βE12 (i.e., cytokeratins 1, 5, 10, and 14) were reported to be consistently expressed in LN, and that this antibody would constitute a useful marker to differentiate between LN and low-grade solid DCIS, there is direct evidence to demonstrate that LN cells do not express cytokeratins 1, 5, 10, and 14, and that 34βE12 expression in LN may be an artifact of antigen retrieval. Hence, caution should be exercised when using the 34βE12 for a diagnosis of LN (21,30).

**E-Cadherin and Related Proteins in Lobular Neoplasia**

LN, including its pleomorphic variant, and ILC are characterized by a dysfunctional E-cadherin-catenin adhesion complex. E-cadherin is a transmembrane adhesion molecule found in adherens junctions and mediates homophilic-homotypic adhesion in epithelial cells; its intracytoplasmic domain is bound to p120 catenin and β-catenin. In breast epithelial cells, loss of E-cadherin results in cytoplasmic,

**FIGURE 22.5 Pleomorphic lobular carcinoma in situ.**

The duct is filled with large, discohesive cells showing apocrine features, intracytoplasmic lumina, and occasional signet ring cells (detailed in insert).
<table>
<thead>
<tr>
<th></th>
<th>LN (ALH/LCIS)</th>
<th>ILC</th>
<th>Low-Grade DCIS</th>
<th>Low-Grade IDC</th>
<th>PLCIS</th>
<th>Pleomorphic ILC</th>
<th>High-Grade ER+ DCIS</th>
<th>High-Grade ER+ IDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/–</td>
<td>+/–</td>
<td>–/+</td>
<td>–/+</td>
</tr>
<tr>
<td>PR</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
</tr>
<tr>
<td>HER2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>Negative</td>
<td>Negative</td>
<td>Membranous</td>
<td>Membranous</td>
<td>Negative</td>
<td>Membranous</td>
<td>Membranous</td>
<td>Membranous</td>
</tr>
<tr>
<td>β-catenin</td>
<td>Cytoplasmic</td>
<td>Cytoplasmic</td>
<td>Membranous</td>
<td>Membranous</td>
<td>Negative</td>
<td>Membranous</td>
<td>Membranous</td>
<td>Membranous</td>
</tr>
<tr>
<td>p120-catenin</td>
<td>Negative</td>
<td>Negative</td>
<td>Membranous</td>
<td>Membranous</td>
<td>Negative</td>
<td>Membranous</td>
<td>Membranous</td>
<td>Membranous</td>
</tr>
<tr>
<td>p53</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
<td>+/+</td>
<td>+/+</td>
<td>–/+</td>
<td>+/+</td>
</tr>
<tr>
<td>Ki-67</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Intermediate/High</td>
<td>Intermediate/High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

- Abnormal patterns can occasionally be seen in the form of discontinuous or fragmented staining or cytoplasmic “dots.”
- Up to 15% of cases display E-cadherin membranous expression.
- Despite the lack of β-catenin membranous expression, nuclear expression is vanishingly rare in LN and PLCIS.
- Approximately 10% of cases may lack membranous E-cadherin expression (87).

ALH, atypical lobular hyperplasia; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; DCIS, ductal carcinoma in situ; PLCIS, pleomorphic LCIS; ER, estrogen receptor; PgR, progesterone receptor; GCDFP-15, gross cystic disease fluid protein-15; LN, lobular neoplasia; –/+, often negative though sometimes positive; +/–, often positive though sometimes negative.
An accurate differentiation between LN and DCIS is of paramount importance, in particular when these lesions are found at the surgical margins. Some validation for using additional evidence to differentiate between LN and DCIS.

**Molecular Aspects of E-Cadherin Inactivation**

One of the most frequent genetic aberrations in ER-positive breast lesions, in particular, those of low histological grade, is 16q loss, which occurs in a high proportion of cases as an early event in the neoplastic development of LN and low-grade DCIS (6,8,10,21,30). While the target gene of 16q deletions in ductal lesions remains to be identified, in lobular lesions, the CDH1 gene, which encodes E-cadherin, has been shown to be the target (8,10,21,30). The mechanisms resulting in CDH1 gene silencing include a combination of genetic, epigenetic, and transcriptional mechanisms. In fact, loss of 16q is usually accompanied by CDH1 inactivating mutations, CDH1 homozygous deletions, and CDH1 gene promoter methylation leading to biallelic silencing of the gene and loss of protein expression (8,21,30).

The study of CDH1 gene mutations in ALH, LCIS, and synchronous ILC has provided direct evidence to suggest that some LN and ILCs are clonally related, given the presence of identical CDH1 gene mutations in the LN and ILC components (8,10,21,30). Consistent with the lack of E-cadherin expression in ALH and LCIS, CDH1 gene mutations have been documented in these lesions; however, some have suggested that these mutations would be less frequent in ALH (47).

One potential explanation for the apparent lower frequency of CDH1 mutations in ALH lies in the challenges posed by the extraction of DNA from samples with small numbers of ALH cells, which are intimately admixed with residual luminal and myoepithelial cells.

In addition to the genetic mechanisms reported to result in CDH1 gene inactivation, there is evidence that E-cadherin expression can be transcriptionally regulated via a number of different transcription factors. Activation of the transforming growth factor β (TGF-β) pathway, and up-regulation of Snail, Slug, and ZEB1 have been reported to result in down-regulation of E-cadherin in lobular lesions (30,45,48). In addition, transcriptomic and immunohistochemical analyses of members of the E-cadherin-catenin complex TWIST and SNAIL revealed that there is a stepwise decrease of the mRNA and proteins of the E-cadherin and catenin families from LCIS to ILC concurrent with up-regulation of TWIST and SNAIL (44).

The strong circumstantial evidence suggesting that CDH1 gene inactivation is a driver of the lobular phenotype has been corroborated by direct evidence from a conditional mouse model, where CDH1 gene mutations and p53 knockout were targeted in an epithelium-specific manner (49). This study revealed that E-cadherin inactivation leads to the genesis of invasive tumors that display the cardinal features of human invasive lobular carcinomas, being composed of dyshesive cells, which infiltrate the mammary gland stroma as single cells and single cell-files, and metastasize to anatomical sites usually affected by ILC, including the gastrointestinal tract, serosal surfaces, and bone (49). It should be noted, however, that lesions consistent with LN were not documented in this animal model and that the pleomorphism exhibited by the cells from the tumors of this animal model, the presence of p53 inactivation, and lack of ER-expression would be consistent with the features of pleomorphic ILC rather than those of the classic variant (50).

Despite the familial predisposition reported for LN, the genes involved in this predisposition remain unclear.
CDH1 germline gene mutations account for approximately 30% of cases of hereditary diffuse gastric carcinoma, which have similar growth features to lobular carcinomas (20,30). Notwithstanding the clear pathogenetic role of somatic CDH1 gene mutations in LN and ILC, germline mutations of CDH1 have been shown to play a limited role in familial LN and ILC. In fact, although ILCs have been reported in the context of hereditary diffuse gastric cancer syndrome, patients with CDH1 germline gene mutations presenting solely with LN and/or ILCs are vanishingly rare (30,51). Cancer predisposition genes, including BRCA1, BRCA2, MLH1, and MSH2, have been reported not to be significantly involved in the pathogenesis of familial lobular neoplasms (30). Intriguingly, an association between CHEK2 U157T mutation and familial predisposition to lobular carcinomas has been reported (52).

Genomics of Lobular Neoplasia

Genome-wide genetic analyses of gene copy number aberrations and allelic changes, as defined by comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays of LN have revealed that these lesions are clonal and neoplastic, that their most frequent copy number changes include 16p, 16q, 17p, and 22q, and gain of material from 6q (6,8,29,30,35,55). In one study, pure ALH harbored a surprisingly high level of genetic instability compared to pure LCIS and lobular lesions from other studies (54). This was interpreted as a mechanism by which most pure ALH develop high-level genetic change and die off, rather than acquire selective genetic changes allowing progression to LCIS and ILC; alternative explanations may stem from the limited amount of input DNA from ALH cells employed in the study. SNP array analyses have recently demonstrated that classic LCIS and a substantial proportion of adjacent synchronous lesions, including ER-positive DCIS, invasive lobular carcinoma, and ER-positive invasive ductal carcinoma, are often clonally related (6). This notion has been further corroborated by CGH studies of matched LCIS and ILC (29), and by the analysis of mitochondrial DNA heteroplasmy and mitochondrial gene mutations (7), which revealed clonal patterns in three out of five ILCs following a diagnosis of LCIS.

PLCIS and pleomorphic ILC are genetically related entities (35,37,55,56), highlighting the potential precursor role of PLCIS in the development pleomorphic ILC akin to the relationship between LCIS and ILC. In situ and invasive pleomorphic lobular lesions have similar genomic profiles to classic LN and ILC, including loss of 16q, and gain of 1q and 16p; however, they do have more complex genomes (35,37,55,56) and amplification of genomic loci involving oncogenes associated with an aggressive phenotype, such as MYC (8q24) and HER2 (17q12) (35,55,56). One study in which PLCIS was sub-classified into those with and without apocrine features suggested that only apocrine, but not conventional PLCIS, would have more gene copy number aberrations than classic LCIS (35); further studies employing an objective definition of this subtype of PLCIS are required to confirm these molecular observations and to determine the clinical significance of these lesions. Importantly, there is evidence, although limited, to suggest that PLCIS and matched invasive pleomorphic ILC are clonally related, based on the similarities of the gene copy number changes they harbor (55).

CLINICAL MANAGEMENT

In current practice, the management of LCIS continues to be a challenge. Although largely accepted as a risk factor for the subsequent development of breast cancer, the long-term cumulative risk and our inability to predict which women will develop breast cancer generates considerable uncertainty among providers, and management options in 2013 remain in the context of observational data. As of 2013, the evidence supporting hormonal therapy to reduce lumpectomy rates of LCIS has shown equivocal findings. In a randomized controlled trial, the 5-year lumpectomy rate for LCIS was somewhat decreased by tamoxifen, but this finding was not statistically significant (57). Among women with breast lesions, there is no evidence-based recommendation regarding surveillance intervals or risk-reduction strategies based on their occurrence alone. As such, a 3-month mammographic follow-up is recommended, with an optional yearly breast MRI if there is a strong suspicion of malignancy. Among women with a strong family history of breast cancer, a shorter duration of surveillance may be considered.
represents a more aggressive subtype, data regarding the natural history of this lesion are limited to two small retrospective reports describing recurrences of PLCIS after excision (31,69). Available data do, however, support routine excision when PLCIS is diagnosed on core biopsy with upgrade rates consistently exceeding 25% (Table 22-3). It should be noted that the small number of cases identified over the span of several years in all of these series suggest that the true incidence of PLCIS is likely quite low.

A diagnosis of classic LCIS or ALH made by surgical excision does not require further surgical intervention, and there is no indication to document margin status in a specimen that contains only LN (21). Similarly, the finding of and there is no indication to document margin status in a

{
<table>
<thead>
<tr>
<th>Series</th>
<th># Excised</th>
<th>% CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgian-Smith and Lawton (59)</td>
<td>5</td>
<td>40%</td>
</tr>
<tr>
<td>Pacelli et al. (63)</td>
<td>5</td>
<td>60%</td>
</tr>
<tr>
<td>Mahoney et al. (62)</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>Lavoue et al. (61)</td>
<td>10</td>
<td>30%</td>
</tr>
<tr>
<td>Carder et al. (88)</td>
<td>10</td>
<td>30%</td>
</tr>
<tr>
<td>Chivukula et al. (89)</td>
<td>12</td>
<td>25%</td>
</tr>
<tr>
<td>Sullivan et al.</td>
<td>LCIS-N = 11</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>LCIS-P = 17</td>
<td>29%</td>
</tr>
</tbody>
</table>

*2 of 10 cases possible “microinvasive carcinoma” on core biopsy.

One-third of cancer cases presented as a “mass” on imaging.

Includes 9 cases identified on E-cadherin staining of DCIS core biopsy cases. PLCIS, pleomorphic LCIS; CA, carcinoma; NA, not applicable; LCIS, lobular carcinoma in situ; LCIS-N, LCIS with necrosis; LCIS-P, pleomorphic LCIS.

Management of the High-Risk Patient

Once a concurrent malignancy has been excluded, women with LCIS should be counseled regarding their increased risk of breast cancer. Compared to the general population, women with LCIS have an eight-fold to 10-fold increased risk of breast cancer (11). In the series with the longest follow-up, the probability of developing carcinoma in situ or invasive cancer was 13% in the first 10 years after diagnosis, 26% after 20 years, and 35% by 35 years, or roughly 1% per year (72). When counseling women about their risk, it is important to stress that the risk remains steady over their lifetimes and that, therefore, the absolute risk of breast cancer for an individual is impacted by their age at LCIS diagnosis. Importantly, however, most women with LCIS will not develop invasive breast cancer.

Surveillance

The NCCN Breast Cancer Screening and Diagnosis Clinical Practice Guidelines for women with LCIS include annual mammography and clinical breast exam (CBE) every 6 to 12 months with consideration of annual MRI (73). Although enhanced breast cancer surveillance strategies that include screening with breast MRI are commonly recommended for women at high risk, the American Cancer Society (ACS) guidelines do not support routine use of MRI in this setting, stating that there is not enough evidence to recommend for or against MRI screening in women at increased risk from LCIS, making the NCCN guideline somewhat difficult to interpret (74). The ACS guidelines are based on the increased sensitivity of MRI
in women at high risk due to an inherited predisposition or strong family history of breast cancer; however, the biology of the breast cancers that develop in women with LCIS differs from those that develop in women at risk on the basis of BRCA mutations, and the optimal screening strategy for women with LCIS remains uncertain.

Until recently, data directly addressing the role of MRI in women with LCIS were limited to two retrospective radiology reports demonstrating that MRI finds mammographically occult cancers in approximately 4% of women with a prior history of LCIS (75,76) and a study from the Memorial Sloan-Kettering Cancer Center (MSKCC) Surveillance program by Port et al. In that study, 252 women with LCIS were included, 135 (54%) of whom were participating in MRI screening (77). The MSKCC experience has now been updated to include 776 patients with LCIS, 59% of whom have been participating in MRI screening, with longitudinal follow-up from 1996 to 2009 (78). This large, well-annotated dataset now includes 98 cancer diagnoses and continues to demonstrate no difference in the crude cancer detection rate among women having conventional screening or conventional screening plus MRI. Taking into account other breast cancer risk factors, length of follow-up, number of MRIs, and the time dependency of breast cancer development, using Landmark Analyses, King et al. further demonstrated that routine use of MRI screening does not result in increased rates of cancer detection in any of the first 3 years following LCIS diagnosis, nor does it result in earlier stage at diagnosis. Not surprisingly, women in the MRI-screened group were significantly more likely to undergo one or more benign biopsies during the surveillance period (36% vs. 13%, \(p < .0001\)), reflecting the low specificity of this imaging modality; a problem that translates to increased patient anxiety and increased health care costs.

Importantly, in this large, modern cohort of women with LCIS followed longitudinally, King et al. also noted that the subsequent invasive cancers that developed were equally divided between those of the ductal and lobular phenotype, and of the 26 lobular cancers that were diagnosed, 10 were diagnosed by MRI imaging, 10 by conventional imaging, and 6 by CBE, reiterating the importance of CBE in this high-risk population. Another pervasive misconception is the propensity of lobular cancers to be bilateral, leading to a strong consideration for contralateral prophylactic mastectomy among women diagnosed with unilateral invasive lobular cancer. Among the 6 LCIS patients in this cohort who developed bilateral breast cancer, none were bilateral lobular cancers. Data from SEER also clearly document that an initial diagnosis of lobular cancer does not increase the risk of a metastatic contralateral cancer compared to patients with ductal disease (79). Finally, this dataset demonstrates that women with classic LCIS, which displays an immunohistochemical profile consistent with that of ER-positive breast cancer, overwhelmingly develop ER-positive breast cancers, which are likely to be detected at small size during routine screening.

Until information on the natural history of PLCIS is available, minimal surveillance strategies for this lesion should include biannual CBE and annual mammography. The decision to incorporate MRI screening should be made on an individual basis following a full discussion of the potential risks and benefits of this approach.

**Chemoprevention**

Prospective randomized data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT, P-1) demonstrated that among high-risk women, tamoxifen decreased the risk of developing invasive breast cancer by 49% (80). Similarly, the NSABP Study of Tamoxifen and Raloxifene (STAR, P-2) demonstrated that raloxifene was just as effective as tamoxifen in reducing the risk of breast cancer in high-risk postmenopausal women (81). Women with LCIS were well represented in both of these studies, comprising 6.2% of 13,338 participants in the P-1 trial and 9.2% of 19,747 participants in the STAR trial. In both subsets, chemoprevention reduced the risk of developing breast cancer by more than 50%. Collectively, these data led to a statement from the American Society of Clinical Oncology (ASCO) recommending 5 years of tamoxifen for high-risk premenopausal women to reduce the risk of ER-positive invasive breast cancer and raloxifene to reduce risk for postmenopausal women. Although there are no data to directly address the use of chemoprevention in PLCIS, the fact that the vast majority of these lesions are ER positive supports a potential role for chemoprevention in patients with this diagnosis.

More recently, the MAP.3 trial demonstrated that compared to placebo, exemestane reduced the risk of invasive breast cancer by 65% in postmenopausal women and appeared to be beneficial in women with a history of ADH, ALH, and/or LCIS (82), and in a large observational study of 2,459 women diagnosed with atypical breast lesions, including LCIS, Coopey et al. reported a significant decrease in breast cancer risk with chemoprevention for all types of atypia (\(p < .001\)), with estimates ranging from a risk reduction of 50% at 5 years to 65% at 10 years. Findings from the MSKCC surveillance program also validate the benefit of chemoprevention in women with LCIS in the clinical setting. Among 998 women, 163 (16%) of whom reported chemoprevention use of at least 6 months, there was a significant reduction in the incidence of breast cancer with chemoprevention, 14.5% versus 3.6% (\(p < .0001\)), at a median follow-up of 84 months (57).

Despite these findings, neither tamoxifen nor raloxifene has been widely embraced, and studies addressing patient and physician attitudes toward chemoprevention are limited. Port et al. found that among 43 high-risk patients offered tamoxifen, 41 declined due to perceived risks (83). Tchou et al. (84) reported a higher acceptance rate of 42% among 137 high-risk women offered tamoxifen, and specifically noted that older age and a history of atypical hyperplasia or LCIS were significant predictors of patient acceptance of tamoxifen at their institution. Collectively, these findings strongly support the need to improve our efforts to educate both high-risk patients and their health care providers about the benefits of chemoprevention in decreasing breast cancer risk.

**Risk-Reducing Surgery**

When LCIS was first described, it was treated as a malignancy necessitating mastectomy like all breast carcinomas at the time, and this remained the standard approach until studies demonstrated that the actual risk of breast cancer was lower than expected and that women with LCIS were equally likely to be diagnosed with ipsilateral or contralateral breast cancers; thus bilateral total mastectomy would be the only logical operation to truly reduce risk. In parallel with the trend toward more conservative therapy for the treatment of invasive breast cancer, aggressive surgical therapy for LCIS fell out of favor and, in the modern MSKCC experience, only a minority of women with LCIS (5%) pursue bilateral prophylactic mastectomy (57). Nevertheless, bilateral prophylactic mastectomy (BPM) may be a reasonable option for a subset of women with LCIS and other risk factors, such as a strong family history or extremely dense breasts.

Historically, BPM was reported to result in an approximately 90% risk reduction for the development of subsequent cancer (85). This figure was based on a retrospective analysis of 639 women with a family history of breast cancer undergoing bilateral prophylactic mastectomies between
1960 and 1993. While it is important to educate patients that prophylactic mastectomy does not completely eliminate cancer risk, many women in this series over time underwent subcutaneous mastectomy, an operation which has fallen out of favor due to the amount of breast tissue frequently left behind, and a more recent retrospective case-cohort study evaluating the efficacy of BPM in a community practice setting reported a 95% risk reduction (86). The current standard of care for prophylactic mastectomy is total mastectomy (with or without reconstruction) with the goal of removing the entire mammary gland as would be performed during therapeutic mastectomy. The desire for nipple preservation in this setting and others is becoming increasingly common, and while this may result in improved cosmesis and patient satisfaction, prospective data supporting this contention and/or the long-term oncologic safety of this approach are not yet available.

Patients considering surgery for risk reduction need to be fully aware of all the risks and benefits of this approach, and should be encouraged to consider the impact that prophylactic surgery may have on their quality of life with respect to body image and sexual functioning. If reconstruction is to be pursued, they should also have a reasonable respect to body image and sexual functioning. If prophylactic surgery may have on their quality of life with and should be encouraged to consider the impact that oncologic safety of this approach are not yet available.

Patients should be informed of their increased risk of breast cancer, and counseled regarding both medical and surgical risk-reducing options. Chemoprevention significantly decreases the risk of breast cancer in patients with LN by at least 50%, and bilateral prophylactic mastectomy reduces the risk of breast cancer by 90% to 95%.

MANAGEMENT SUMMARY

- LCIS and ALH are uncommon pathologic findings, representing a part of a spectrum of epithelial proliferations referred to as LN. They are typically incidental findings, identified in up to 4% of otherwise benign breast biopsies, yet, given that they have no distinctive clinical presentation or imaging features, the prevalence of LCIS likely exceeds its incidence.

- A diagnosis of LCIS confers a long-term cumulative risk of subsequent breast cancer that averages 1% to 2% per year and remains steady over time, resulting in relative risk of breast cancer that is eight-fold to 10-fold greater than the general population risk. ALH is associated with a relative risk of breast cancer four-fold to five-fold greater than the general population.

- Routine surgical excision following a core biopsy diagnosis of LN is supported by NCCN guidelines; however, emerging data support observation in cases in which there are no other indications for excision, and radiographic-pathologic concordance has been confirmed by multidisciplinary review. A core biopsy diagnosis of PLCIS should be followed by surgical excision due to the high rates of associated cancer in reported series.

- A diagnosis of PLCIS made by surgical excision does not require further surgical intervention; there is no indication to document margin status in specimens that contain only LN. The presence of LN in a lumpectomy specimen or at the margin is not a contraindication to breast conservation and does not require re-excision.

- Given the available data, it is reasonable to attempt complete excision to a negative margin for cases of PLCIS. However, there are no data to support the efficacy of radiation therapy for this diagnosis.

REFERENCES


