# Lobular neoplasia

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**Abstract**

Although pathologists have recognized the classic forms of lobular neoplasia for decades, our understanding of this disease has changed markedly since its first description. The term lobular neoplasia encompasses a spectrum of entities ranging from atypical lobular hyperplasia to more recently recognized lobular carcinoma in situ (LCIS) variants including LCIS with necrosis and pleomorphic LCIS. Along with an expanded definition of lobular neoplasia, our concept of the pathobiologic potential of these lesions has evolved. While lobular neoplasia has been viewed primarily as a risk marker of invasive breast carcinoma since the late 1970s, there is increasing evidence that they are also non-obligate precursors. In this review, we will address the history of the disease, updated concepts and histologic definitions, and advances in immunohistochemistry and molecular pathology that have shaped both the way we diagnose and manage lobular neoplasia.

**Keywords** atypical lobular hyperplasia; e-cadherin; lobular carcinoma in situ; lobular carcinoma in situ variants; lobular neoplasia; pleomorphic lobular carcinoma in situ

## Introduction

Lobular carcinoma in situ (LCIS) was first characterized as a distinct entity by Foote and Stewart in 1941[1] who described LCIS as a non-invasive cancerous lesion arising in lobules and composed of uniform small cells with cytologic features similar to invasive lobular carcinoma (ILC). Atypical lobular hyperplasia (ALH) was subsequently defined as a similar lesion but with a lesser degree of lobular involvement.[2]

The term lobular neoplasia (LN) was proposed by Haagensen in 1978 in place of LCIS in order to avoid the word ''carcinoma'', as this often triggered a mastectomy, a practice Haagensen did not support for this ''benign non-infiltrating lobular proliferation''.[3] Since then, the term LN has been used to encompass ALH and LCIS and has been adopted by organizations like the World Health Organization.[4] Tavassoli further modified the LN nomenclature by introducing the terminology of lobular intraepithelial neoplasia (LIN). LIN is a three tiered grading system based on cytologic features and the degree of lobular distention. The LIN grade also reflects the clinical behavior; in contrast to LIN1, LIN3 is frequently associated with invasive carcinoma and warrants different management.[5]

An association between LN and ILC has been recognized since the first description of LN. Originally, LN was thought of as a preinvasive malignancy with the potential to progress to invasive carcinoma. Therefore, mastectomies — often bilateral — were the mainstay of treatment. In the late 1970s, our view of LN began to change. The work of Haagensen, Rosen, and Page all highlighted the indolent behavior of LN, suggesting that LN was a risk factor, rather than a true precursor lesion.[2,3,6,7] Their studies showed that overall, 19% of patients originally diagnosed with LN, LCIS or ALH in an excisional biopsy developed subsequent breast carcinoma after a long-term follow-up period. Follow-up time ranged from 14 to 24 years with an average of 18 years (Table 1). The relative risk of subsequent carcinoma was found to be 4-times and 9-times greater in patients with ALH and LCIS respectively, compared to women with non-proliferative breast disease. An accompanying family history of breast carcinoma doubled this risk. It was noted that patients went on to develop their subsequent cancer in either breast and that this cancer was often of ductal rather than lobular type, providing further support for the risk marker theory. The risk of subsequent carcinoma was long lasting; in one of the studies, approximately one third of subsequent cancers developed more than 20 years after the original diagnosis of LN.[6] With this knowledge, the treatment of LN shifted significantly with observation rather than surgery becoming the standard of care.

More recent studies have also pointed to a precursor role for LN. The laterality of subsequent cancers in LN patients was shown to be more likely on the side of LN diagnosis[8] and a higher percentage of patients with a history of LN were found to develop ILC versus invasive ductal carcinoma compared to the general population of women with breast cancer.[9,10] The recognition of LCIS variants (LCIS with necrosis - NLCIS, pleomorphic LCIS - PLCIS) and various molecular studies also point to a precursor role for LN. While we now understand that LN is a heterogeneous group of lesions with various pathologic and clinical characteristics, the management of LN is still evolving and there are no comprehensive guidelines for the management of these lesions.

## Epidemiology and clinical presentation

Most of our knowledge of LN is derived from studies on ALH and classic LCIS. LN is most commonly detected in premenopausal women, is multifocal and tends to be multicentric and bilateral in about 50% of cases.[11,12] Classic LN is most often diagnosed as an incidental finding, however, it can present with indeterminate punctate calcifications.[13]

The incidence of LCIS is difficult to establish. The incidence of LN diagnosed in benign excisional biopsies (no invasive carcinoma or ductal carcinoma in situ in the specimen) has been reported to range from 0.5 to 3.8% (Table 1). In comparison, a large multi-institutional retrospective study on the underestimation of LN on core biopsy showed ALH and LCIS represented 0.9% of breast core biopsies ($n = 32420$).[14] During a more recent short-term study (18-month period, 2007–2008) at a single

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**Subsequent carcinoma in women with lobular neoplasia treated only with surgical biopsy**

| Study | Diagnosis | Incidence[a] | Follow-up (years) | Subsequent carcinoma | RR |
|---|---|---|---|---|---|
| Page[2] | ALH | 1.6 | 17 | 16/126 (13%) | 4.2 |
| Haagensen[3] | LN | 3.8 | 14 | 36/210 (17%) | 7 |
| Rosen[6] | LCIS | 1.3 | 24 | 28/84 (33%) | 9 |
| Page[7] | LCIS | 0.5 | 18 | 9/39 (23%) | 9 |
| Total | | | | 89/459 (19%) | |

ALH, atypical lobular hyperplasia; LN, lobular neoplasia; LCIS, lobular carcinoma in situ; RR, relative risk.
[a] Incidence in "benign" biopsies (without ductal carcinoma in situ or invasive carcinoma).

**Table 1**

institution, LCIS was found in 2% of all ($n = 3203$) breast core biopsies.[15] In the United States, the incidence of LCIS increased significantly from 1978 to 1998, specifically in post-menopausal women,[16] while more recently, there has been no clear trend.[17] The use of and subsequent decrease in use of combination hormonal replacement therapy (HRT) has been implicated in this incidence pattern as HRT was shown to have a similar effect on the incidence of ILC.[18]

## Morphology

Most of the originally described features of LCIS are still valid today. Classic LCIS (CLCIS) consists of a uniform population of discohesive small cells with intracytoplasmic lumens and mucin vacuoles (Figure 1). The cells of CLCIS can be further categorized as type A or type B. Type A cells are small with nuclear size up to 1.5-times a lymphocyte and have inconspicious nucleoli. Type B cells display larger nuclei, more abundant cytoplasm and may show a minimal degree of pleomorphism.[3] Clinical implications of type A and B cytologic variations have not yet been demonstrated. Although the cellular features of type B cells in LN can resemble grade 2 ductal carcinoma in situ (DCIS), to date, no stratification based purely on nuclear grade has been proposed for LN. Additional rare variations of LN morphology have been described, such as clear cell, histiocytoid, apocrine, and signet ring cell.[19]

Various criteria exist for distinguishing ALH from LCIS. One of the most frequently cited thresholds for separating the two entities is that of Page which requires the filling and distention of at least 50% of the lobular units to diagnose LCIS. Distention is arbitrarily defined as a proliferation more than seven cells thick.[2] Rosen advocates involvement of at least 75% of the units of a lobule by the lobular proliferation before the diagnosis of LCIS can be rendered.[19] In contrast to these purely quantitative divisions, Tavassoli's classification uses a combination of quantitative and qualitative criteria and has more complex clinical implications. LIN1 shows partial to complete filling of terminal ducts or lobular units by characteristic LN cells without distention. LIN2 shows some distention and in LIN3 the distention is so marked that the lobular units appear confluent. Importantly, specific cytologic features such as necrosis, signet ring cell morphology or pleomorphism place a lesion into the LIN3 category even in the absence of marked distention.

## Lobular neoplasia variants

While classic LN encompasses entities known for nearly a century, a small fraction of LN consists of more recently described variants including NLCIS and PLCIS that have morphologic, biologic and clinical features differing from classic LN. While PLCIS is well known with a fair amount of literature on the subject, NLCIS remains a relatively obscure entity with a dearth of literature. Tavassoli acknowledged comedo necrosis as a feature of LCIS almost 20 years ago.[20] Despite this fact, NLCIS has yet to be widely recognized as a discrete entity and is often diagnosed as DCIS or mixed CIS (MCIS).[21,22] NLCIS has the cytologic, architectural and immunophenotypic features of CLCIS and often features prominent distention of the glandular spaces by neoplastic cells. The necrosis may be punctate or comedo-type (Figure 1).[21] In 2000, Sapino described 10 cases of LCIS with pleomorphic calcifications, a mammographic presentation traditionally associated with DCIS; 4 of these cases were associated with ILC.[23] Along with marked distention of glandular spaces and necrosis, these cases demonstrated the characteristic uniform discohesive cells with intracytoplasmic mucin and E-cadherin negativity. Based on illustrations included in the paper, some also included tumor cells with pleomorphism. In a later review of 18 cases of NLCIS diagnosed in either core biopsy or in surgical specimens, half were associated with adjacent ILC.[21]

PLCIS consists of a variably discohesive population of pleomorphic medium to large cells with eccentrically placed nuclei at least 4 times the size of a lymphocyte and with distinct to prominent nucleoli (Figure 1).[24] Marked distention, necrosis and microcalcifications are frequently present, but are not necessary for the diagnosis of PLCIS. Although the cytologic features of PLCIS can strongly resemble DCIS, the discohesive architecture, intracytoplasmic mucin with targetoid inclusions, and frequent presence of adjacent CLCIS should point to the lobular nature of the proliferation and prompt confirmation by immunohistochemistry (IHC). Similar to NLCIS, almost one half of the cases collected by Sneige were associated with ILC.

The overlap in the histologic features of NLCIS and PLCIS can cause diagnostic confusion. For example, necrosis can be associated with PLCIS and occasional pleomorphic cells can be seen in NLCIS. These overlapping criteria and the lack of precise definitions often result in the diagnosis of