by Haagensen as *type B cells*[32] (Fig. 2). LCIS is typically present in the terminal duct lobular units and distends and distorts the involved spaces. In some instances, LCIS cells involve extralobular ducts. The growth within these ducts may be either solid or pagetoid (i.e., the LCIS cells are insinuated between the duct basement membrane and the native ductal epithelial cells). Although some authors previously recognized a cribriform pattern of involvement of extralobular ducts by LCIS,[33] *in situ* lesions with a cribriform pattern are probably best categorized as DCIS.

Cell kinetic studies have shown that LCIS has a low proliferative rate.[34–36] The cells of LCIS are also typically estrogen-receptor positive[35–37] and rarely, if ever, show overexpression of the *c-erb*-b2 (*HER-2/neu*) oncogene[35,36,38,39] or accumulation of the p53 protein.[35,36] In addition, studies have indicated that the cells of LCIS are characterized by loss of expression of the adhesion molecule E-cadherin.[40]

DIFFERENTIAL DIAGNOSIS

The cells composing atypical lobular hyperplasia are similar to those that characterize LCIS, but in atypical lobular hyperplasia the degree of involvement of the terminal ducts and lobules is less extensive. Unfortunately, no sharp dividing line exists between atypical lobular hyperplasia and LCIS, and diagnostic criteria for this distinction vary among experts. Some authors require that at least 50% of the spaces in a given lobule be filled with and distended by the characteristic cells to warrant a diagnosis of LCIS,[27] whereas others do not consider lobular distention and enlargement an essential feature for the diagnosis of LCIS.[28] In some patients, LCIS may involve areas of breast tissue that have preexisting benign alterations; for example, LCIS may involve foci of sclerosing adenosis and produce a pattern that mimics invasive carcinoma.[41] However, low-power examination of such specimens usually reveals the lobulocentric configuration characteristic of adenosis. Finally, as discussed in Chapter 27, in the section dealing with the pathology of DCIS, sometimes the distinction between LCIS and DCIS is problematic.[42–45]

NATURAL HISTORY AND TREATMENT

The major issue in the management of LCIS is the risk of invasive carcinoma after a diagnosis of LCIS. Treatment strategies have varied depending on whether LCIS was considered to be the anatomic precursor of invasive carcinoma, an obligate premalignant lesion, or simply a marker for an increased risk of breast cancer development. Six series[2–5,12,46] with long-term follow-up address the malignant potential of LCIS after biopsy alone (Table 1). Patients with LCIS and without associated invasive carcinoma were studied, although women who had contralateral invasive carcinoma before receiving a diagnosis of LCIS were included in some reports, making calculation of the incidence of invasive carcinoma difficult. The largest series, reported by Haagensen et al.,[3] included 287 women monitored for a mean of 16.3 years, with only 2 patients lost to follow-up. Breast cancer developed in 63 patients (21% of those in the series). If the 10 patients whose LCIS diagnosis followed treatment for contralateral invasive breast cancer are excluded, 18% of the women developed carcinoma, a ratio of observed to expected cases of 6.9 to 1.0. In a similar study from Memorial Hospital, Rosen et al.[12] identified 99 patients with LCIS who were monitored for a mean of 24 years, although complete follow-up was available for only 84 women. Twenty-nine women subsequently developed invasive carcinoma (34.5%); however, if all the patients lost to follow-up are considered free of disease, this figure falls to 29.2%. The relative risk of breast cancer development in this series was 9, the same level of risk observed by Page et al.[2] in a report of 44 cases of LCIS followed for 18 years. Page's group, however, observed that the risk of developing infiltrating carcinoma was greatest during the first 15 years after biopsy (relative risk, 10.8) and decreased to 4.2 for those women remaining free of carcinoma for 15 years. In contrast, Rosen et al.[12] observed no decrease in the risk of development of invasive carcinoma during their 24-year follow-up period. Wheeler et al.[4] and Andersen[5] reported the development of invasive carcinoma in 12.5% and 26.4% of women monitored for 17.5 and 15 years, respectively. In two other studies,[47,48] similar levels of risk associated with LCIS were noted. Salvadori et al.[47] reported on 80 women with LCIS who were monitored for a median of 58 months. Five cases of invasive carcinoma (6.3%) were noted, a ratio of observed to expected cases of 10.3 to 1.0. Sixty-nine cases of LCIS were identified in a prospective study by the Danish Breast Cancer Cooperative Group[48]; at a median follow-up of 61 months, 8 infiltrating carcinomas had occurred (11.6%). The relative risk of cancer development among women with LCIS in this study was 11.

In contrast, a study of 182 women with LCIS reported by Fisher et al.[45] noted only a 3.3% incidence of invasive carcinoma after 5 years of follow-up. The authors note that these lesions were excised to negative margins because they were initially diagnosed as DCIS and suggest that this may be the factor responsible for the low incidence of invasive carci-

TABLE 1. *Follow-up of patients diagnosed with lobular carcinoma* in situ

Study	*n*	Invasive cancer (%)	Follow-up (yr)	Relative risk
Haagensen et al.[3]	287	18	16.3	6.9
Rosen et al.[12]	99	34.5[a]	24	9.0
Wheeler et al.[4]	32	12.5	17.5	—
Andersen[5]	47	26.4[b]	15	12.0
Page et al.[2]	44	23	18	9.0
Salvadori et al.[47]	80	6.3	5	10.3
Ottesen et al.[48]	69	11.6	5	11.0
Bodian et al.[46]	236	26[c]	18	5.4
Fisher et al.[45]	182	3.3	5	—

[a]Percentage calculated for 85 patients with follow-up.
[b]Includes two patients with bilateral cancers counted separately.
[c]Includes ductal carcinoma *in situ* and invasive carcinoma.