Diagnosis and Management of High-Risk Breast Lesions

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Abstract

Atypical hyperplasia (AH) and lobular carcinoma in situ (LCIS) are nonmalignant breast lesions that confer a 4- to 10-fold increased risk for breast cancer in women. Often, AH and LCIS are diagnosed through breast biopsy due to a mammographic or palpable finding. Although AH and LCIS are benign breast disease, further management is necessary due to their high-risk nature and premalignant potential. Over the decades, management of AH and LCIS has changed as more is learned about these disease processes. This review explores the studies evaluating the risk for breast cancer in women with AH or LCIS and the clinical management of these lesions, which can include a combination of surgical excision, surveillance, and risk-reduction therapy.

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Benign breast disease is often diagnosed through biopsy performed as a result of concerning mammographic or palpable findings. More than 1 million US women undergo breast biopsies annually due to these concerns, with >70% of the results revealing benign disease.¹ However, not all benign breast biopsies are equal, and certain lesions confer an increased risk for breast cancer. Specifically, lesions with atypical hyperplasia (AH) and lobular carcinoma in situ (LCIS) have been shown to be associated with a higher risk for future breast cancer and to be precursors in breast carcinogenesis.^{2–5} Recent data have also shown a high cumulative breast cancer incidence of 30% at 25 years of follow-up in women with AH.³

Management of these high-risk lesions is essential in breast cancer prevention. This review discusses the clinical presentation and histologic diagnosis of AH and LCIS, and examines the risk for invasive breast cancer associated with and management of these lesions, including surgical excision, surveillance, and risk-reduction therapy.

Clinical Presentation and Histologic Features

In the initial study by Dupont and Page,⁶ which noted that breast lesions with atypia carried a higher risk for breast cancer, breast biopsies were predominately performed on palpable masses and only 3.6% of the biopsies showed atypia. In the current era of breast cancer screening with digital mammography, recent studies have shown that approximately 10% of all benign breast biopsies show AH.⁷ In a study evaluating biopsies performed as a result of calcifications noted on mammogram, AH was detected in 12% to 17% of patients.⁸ AH and LCIS lesions often present as a mammographic abnormality, indicating the importance of breast cancer screening with annual mammogram to identify high-risk patients.

Atypical ductal hyperplasia (ADH) is defined as distended ducts filled with a proliferation of monotonous epithelial cells with round nuclei forming architecturally complex patterns.⁹ Low-grade ductal carcinoma in situ (DCIS) contains similar histologic features to ADH but tends to be more exten-

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sive. Since differences in diagnosis of ADH or DCIS is dependent on the extensiveness of disease, surgical excision is often recommended for a definitive diagnosis. Atypical lobular hyperplasia (ALH) is composed of monomorphic cells that are round or oval and usually evenly spaced with eccentric nuclei and lack cohesion.⁵ They are present in fewer than one-half of the acini of a lobular unit that is distorted or distended. LCIS is similar to ALH but contains more extensive disease and is associated with a higher risk of breast cancer. Loss of the cell–cell junction protein, E-cadherin, is noted in ALH, LCIS, and invasive lobular carcinoma and can help distinguish from ductal phenotypes through immunohistochemistry. Estrogen receptor (ER) expression was evaluated by Barr et al¹⁰ in AH and found that 97% of ADH lesions and 88% of ALH lesions were positive for ER staining in ≥10% of the cells.

Risk of Breast Cancer

In 1985, Dupont and Page⁶ showed an elevated risk for breast cancer in women with AH and LCIS using the Nashville Breast Cohort, in which they followed >3,000 women with benign breast biopsies. They found that women with proliferative breast disease and atypia had a relative risk (RR) of 5.3 (95% CI, 3.1–8.8) compared with those without atypia. Similar findings have been confirmed in other cohorts (Table 1). The absolute risk for breast cancer is approximately 1% to 2% per year for women with ALH and ADH and 2% per year in those with LCIS.^{11–13} Coopey et al¹¹ estimated a 10-year risk of breast cancer of 21% in these women. Hartmann et al^{3,5} followed women in the Mayo Clinic Benign Breast Disease cohort and found a cumulative incidence

of 30% for invasive breast cancer after 25 years of follow-up in those with AH or LCIS. These recent findings confirmed previous studies and indicate that the risk persists long-term.

Risk Modifiers

Multiple studies have evaluated whether clinical or histologic factors modify the risk of breast cancer in patients with AH/LCIS. Age at AH diagnosis has been shown to affect risk, with those diagnosed at a younger age, such as premenopausal women, more likely to develop breast cancer.^{3,14} However, recent data from Mazzola et al¹⁵ showed that the 15-year cancer risk in women with atypia was not significantly different among various age groups. Family history of breast cancer has been evaluated in women who also have AH/LCIS, with mixed findings reported. Dupont and Page⁶ noted that a subset of women with AH and a family history of breast cancer had an RR of breast cancer of 8.9 (95% CI, 4.8–17) compared with 3.5 (95% CI, 2.3–5.5) in women with AH and no family history. However, data from the Nurses' Health Study and Mayo Clinic Benign Breast Disease Cohort did not show a significant difference in RR of breast cancer due to family history in women with AH.^{3,16}

Increased mammographic density has been noted to be an independent risk factor for breast cancer. Ghosh et al¹⁷ evaluated the association between mammographic breast density and benign breast disease. They assessed breast density using BI-RADS categories and found that increased breast density was noted in those with high-risk breast lesions, such as ALH. Women with ALH had a 50% greater chance of having dense breasts than

Table 1. RR of Breast Cancer After Diagnosis of AH					
Study	N	Median Follow-Up Duration, y	RR of Breast Cancer (95% CI)		
			ADH	ALH	All AH
Nashville Breast Cohort, 1985 ^{6,50}	232	17	4.7 (2.5–8.9)	5.8 (3.0–11.0)	4.4 (3.1–6.3)
Nurses' Health Study, 1992 ¹⁴	74	8	–	–	3.7 (2.1–6.8)
Nurses' Health Study, 2007 ¹⁶	96	9.1	3.09 (2.01–4.75)	5.49 (3.29–9.18)	4.11 (2.9–5.83)
Henry Ford Health System, 2007 ⁵¹	246	–	5.0 (2.3–11.0)	3.2 (0.83–12.4)	4.6 (2.93–7.37)
Mayo Benign Breast Disease Cohort, 2014 ³	698	12.5	3.93 (3.0–5.06)	4.76 (3.74–5.97)	4.34 (3.66–5.12)
Breast Cancer Surveillance Consortium, 2017 ¹²	1,727	10	2.6 (2.0–3.4) ^a	–	–

Abbreviations: ADH, atypical ductal hyperplasia; AH, atypical hyperplasia; ALH, atypical lobular hyperplasia; RR, relative risk.
^aHazard ratios reported.

those without (odds ratio, 1.5; 95% CI, 1.2–2.1; $P=.05$), but ADH was not found to be associated with dense breast tissue.¹⁷ An association between breast density and risk of breast cancer in women with AH was not found.¹⁸

Histologic features, such as number of foci affected and involution of lobules, have been shown to stratify the risk of breast cancer in women with AH. Hartmann et al^{3,5} showed an increase in the cumulative incidence of breast cancer in women with AH, with increasing number of separate foci affected with atypia. Women with ≥ 3 atypical foci had a 46.6% risk of breast cancer at 25 years compared with 23.9% in women with 1 atypical foci. Involution or regression of the lobules in the background breast tissue in women with AH has also been shown to affect breast cancer risk. Women with greater lobular involution in the background breast tissue had a decreased RR of breast cancer (RR, 1.49; 95% CI, 0.41–3.82) compared with those with no involution (RR, 7.79; 95% CI, 3.56–14.81).¹⁹

Risk Models

Risk models currently available, such as the Gail model (Breast Cancer Risk Assessment Tool) and the Tyrer-Cuzick model, incorporate AH into their models and risk predictions but do not provide accurate estimates for these high-risk women. The Tyrer-Cuzick model has been shown to overestimate the risk of breast cancer in women with AH, whereas the Gail model was found to underestimate this risk.^{20,21} Degnim et al²² used the Mayo Clinic Benign Breast Disease Cohort to develop a new model for breast cancer risk in these women, and validated it using the Nashville Breast Cohort. Variables included in the model were age at biopsy, age at biopsy squared, and number of foci with atypia. Ten-year risk estimates showed that the model demonstrated good discrimination (0.63; 95% CI, 0.57–0.70) and acceptable discrimination in the validation set with the Nashville Breast Cohort (0.59; 95% CI, 0.51–0.67).²² These risk models will help inform both future discussions of individual risk for breast cancer with patients and further interventions between physicians and patients with AH.

Features of Subsequent Breast Cancers

Women from the Mayo Clinic Benign Breast Disease Cohort have been followed for the development of subsequent breast cancers, with a median follow-up of 15.8 years.²³ Ipsilateral breast cancers were predominant to the side of the previous benign breast biopsy in women with AH, suggesting that AH is a precursor lesion in the development of invasive breast cancer. Time to development of DCIS from previous benign biopsy was shorter versus time to development of invasive breast cancer, which further suggests the pathway of progression to invasive breast cancer. Women with AH were also noted to be more likely to have ER-positive and progesterone receptor-positive disease.^{5,23}

Clinical Management

Surgery

The upgrade rate of ADH becoming DCIS or invasive breast cancer on excisional biopsy ranges from 18% to 31%.^{24,25} Because the differences between ADH and DCIS are mainly the extent and size of the disease, excisional biopsy is often warranted for a definitive diagnosis. Standard of care is to excise all ADH lesions due to the higher upgrade rate and concern for DCIS. Recent literature has noted that some patients with ADH may opt for conservative management. Nguyen et al²⁶ evaluated the clinical, mammographic, and histologic features of 140 patients with ADH diagnosed through vacuum-assisted breast biopsy (VABB) to determine factors that may predict presence of carcinoma. They found that the number of calcifications removed during biopsy ($<95\%$) was significantly associated with the rate of upgrade of ADH to carcinoma. Histologic features, such as number of terminal duct lobular units (TD-LUs, >2), presence of significant cytologic atypia suspicious for carcinoma, and necrosis, were significantly correlated with a higher upgrade rate. Cases without these features were associated with an approximately 3% risk of carcinoma.²⁶ Similar criteria were identified by investigators at Mayo Clinic, who noted an upgrade rate of 5% among patients with ADH with the low-risk features.²⁷

Menen et al²⁸ reported on long-term follow-up of patients who underwent conservative management versus those who underwent surgical excision using

these identified criteria. Using a multidisciplinary approach, they identified patients with ADH who were at low risk for upgrade and recommended conservative management and surveillance. Of 175 patients with ADH, 125 were observed and 50 underwent excision, and a total of 14 breast cancer events were noted after a median follow-up of 3 years. A total of 6 women (12%) in the surgery group developed breast cancer and 7 cancers (5.6%) were noted in the observation group.²⁸

Schiaffino et al²⁹ showed similar findings in their cohort of 65 patients with ADH who underwent VABB and did not have residual calcifications after biopsy and underwent conservative management. Mean follow-up was 67 months and only 1 patient developed low-grade DCIS, revealing an upgrade rate of <2%. Although standard of care is to surgically excise ADH, conservative management of select cases should be considered.

Surgical management of ALH/LCIS can be controversial. Previous studies have noted an upgrade rate to DCIS or invasive carcinoma of up to 50% in patients with lobular neoplasia, which led to the recommendation of surgical excision for all patients with ALH and LCIS.³⁰ The limitations of early studies were selection for higher-risk cases for surgery and no evaluation for radiologic-pathologic discordance. Recent studies have shown that factors associated with a higher upgrade rate on excisional biopsy included extent of disease (>3 TDLUs), whether the lobular lesion was target of initial biopsy, and suspicious findings on imaging.^{31–36} Incidental findings of lobular neoplasia on core biopsy was associated with a lower upgrade rate to carcinoma, and observation is recommended.³¹ Additionally, radiologic and pathologic concordance needs to be determined for consideration of conservative management.

Surveillance

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Screening and Diagnosis delineate the recommendations for screening high-risk populations, including women with AH and LCIS.³⁷ Annual screening mammogram with consideration for tomosynthesis is recommended starting at time of diagnosis of ADH/ALH or LCIS, but not in women aged <30 years. Due to the elevated risk for breast cancer, clinical breast examination is recommended every 6 to 12 months.

Screening with breast MRI was previously recommended for women with elevated risk for breast cancer predominately due to family history of breast cancer, but did not include those with history of AH or LCIS.³⁸ Due to insufficient evidence to make a recommendation for or against breast MRI screening in this high-risk population, American Cancer Society guidelines recommend discussion with healthcare provider, whereas NCCN Guidelines recommend considering a breast MRI for screening due to emerging evidence.^{37,39,40} Automated breast ultrasound has been evaluated for breast cancer screening as an adjunct to mammography in women with dense breast tissue, but further investigation is needed for those with AH/LCIS.⁴¹ Molecular breast imaging is also currently being evaluated as an imaging modality to identify breast malignancies in women with AH/LCIS (ClinicalTrials.gov identifier: NCT00620087).

Risk Reduction Therapy

Multiple studies have evaluated selective ER modulators (SERMs) and aromatase inhibitors (AIs) for the prevention of breast cancer. The Breast Cancer Prevention Trial (BCPT) evaluated 13,388 women aged ≥35 years with an elevated risk of breast cancer randomized to tamoxifen daily for 5 years or placebo. Tamoxifen reduced the incidence of invasive breast cancer by 49% ($P<.0001$) and of noninvasive breast cancer by 50% ($P<.002$).⁴² Among specific high-risk groups, tamoxifen reduced the incidence of breast cancer by 56% in women with LCIS and 86% in women with AH. Tamoxifen reduces the incidence of ER-positive tumors, and we have seen that AH and LCIS often progress to ER-positive breast cancers.

The Study of Tamoxifen and Raloxifene (STAR) trial found that raloxifene showed a similar risk reduction of invasive breast cancer compared with tamoxifen after 5 years of therapy. On long-term follow-up of 81 months, tamoxifen was noted to be 25% more effective than raloxifene, and had a more durable response. Subset analysis of its preventive effects in women with AH/LCIS showed that raloxifene and tamoxifen were equivalent.⁴³ AIs such as exemestane and anastrozole have also been evaluated in the MAP.3 and IBIS-2 trials, respectively. Exemestane daily versus placebo daily for 5 years showed a benefit in RR of breast cancer of 0.35 (95% CI, 0.18–0.70) and 0.61 (95% CI, 0.20–1.82) in women with AH and LCIS, respectively, although

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Table 2. Randomized Trials of Antiestrogen Therapy in High-Risk Women and Those With AH/LCIS

Trial	N	Agents	Median Follow-Up, mo	RR for Invasive Breast Cancer (95% CI)	RR for AH or LCIS (95% CI)
NSABP-1 ⁴²	13,388	Tamoxifen vs placebo	84	0.57 (0.46–0.70)	0.25 (0.10–0.52)
STAR ⁴³	19,747	Raloxifene vs tamoxifen	81	1.24 (1.05–1.47)	Long-term tamoxifen provides greater risk reduction
IBIS-1 ⁵²	7,154	Tamoxifen vs placebo	192	0.71 (0.60–0.83)	Not reported
MAP.3 ⁴⁴	4,560	Exemestane vs placebo	35	0.35 (0.18–0.70)	0.61 (0.20–1.82)
IBIS-II ⁴⁵	3,864	Anastrozole vs placebo	60	0.50 (0.32–0.76)	0.31 (0.12–0.84)

Abbreviations: AH, atypical hyperplasia; LCIS, lobular carcinoma in situ; RR, relative risk.

sample size was small for this subset.⁴⁴ Anastrozole given daily for 5 years was also shown to be effective in reducing incidence of breast cancer in postmenopausal women with AH or LCIS (RR, 0.31; 95% CI, 0.12–0.84).⁴⁵ Table 2 summarizes the randomized trials of SERMs and AIs and their risk reduction of invasive breast cancer in these high-risk populations, and highlights that these medications provide the greatest benefit to women with AH or LCIS. Coopey et al¹¹ reviewed 2,938 cases with atypical breast lesions and determined that the estimated 10-year risk of women with AH who did not receive preventive therapy was 21.3%, whereas those who received preventive therapy had a 10-year risk of 7.5% ($P < .001$), revealing a significant reduction in breast cancer risk for women with AH and a need to recommend therapy. Clinical trials evaluating metformin and a novel somatostatin analog are ongoing as potential preventive therapy agents for women with AH or LCIS (ClinicalTrials.gov identifiers: NCT01905046, NCT01372644).

Despite the findings from these clinical trials showing the benefit of SERMs and AIs in preventing breast cancer, uptake of these medications is low. Waters et al⁴⁶ noted that the uptake among US women was dismal at 0.2%. Uptake was higher in academic centers, ranging from 13% to 25% in women with AH/LCIS, but there is still need for improvement.^{47,48} Our practice evaluated a performance improvement program that assessed women with AH/LCIS, including whether they were recommended and prescribed preventive therapy. Feedback regarding the data collected was given to individual providers with the goal of increasing the recommendation and uptake of preventive therapy. With this approach, 98% of women diagnosed with AH or LCIS were recommended preventive therapy, and uptake was 82% in

newly diagnosed patients and 48% in patients who were previously diagnosed but may have declined preventive therapy in the past.⁴⁹ Presentation of the recent data showing increased risk of breast cancer in this population,^{3,5,11–13} together with our strong recommendation and the significant benefit of these medications shown in these women, has increased uptake in our center, and this approach should be considered in other clinics as well.

Conclusions

AH and LCIS have an increased RR of breast cancer and a cumulative incidence of breast cancer of 30% at 25 years, leading to a 1% to 2% increase per year. Age at diagnosis and number of atypical foci have been shown to modify risk estimates in individuals with AH/LCIS, but accurate risk assessments to identify those who will develop breast cancer are still lacking. Education of women diagnosed with AH/LCIS should involve discussion of the population risk until better individual risk estimates can be developed.

Management of women with AH/LCIS using surgical excision is changing, with more data suggesting multidisciplinary review and evaluation for radiologic and pathologic concordance should be used to identify patients for conservative management. Women should continue to undergo screening mammograms, and breast MRI should also be discussed and considered in this population. Finally, risk-reduction therapy with SERMs and AIs has been shown to have a significant effect in these women, and therefore it is important to review these benefits with patients and increase uptake of these medications.

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