Curr Radiol Rep (2018) 6:7
https://doi.org/10.1007/s40134-018-0268-6

Current Management of High-Risk Breast Lesions

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Published online: 30 January 2018

Abstract
Purpose of review The purpose of this review is to describe recent updates in the management of high-risk breast lesions. We review the various high-risk breast lesions and evaluate the collective literature regarding the rates of upgrade to invasive cancer or ductal carcinoma in situ with excisional biopsy as well as the increased risk for future breast cancer development that a diagnosis of a high-risk breast lesion may portend. For those lesions associated with an increased risk of breast cancer, we discuss the appropriate surveillance regimens as well as risk reduction opportunities available to patients.
Recent findings Recent studies may suggest a role for close imaging observation in certain clinical settings when a benign intraductal papilloma or flat epithelial atypia is identified by core needle breast biopsy. Ongoing prospective clinical trials should reveal valuable data to help answer this question.
Summary Clinical management of high-risk breast lesions identified and determined to be concordant after image-guided core needle biopsy varies and prospective data are needed to better guide management decisions. High-risk breast lesions require close radiologic-pathologic correlation when diagnosed by image-guided breast core needle biopsy. Excisional biopsy can exclude a higher-grade lesion such as DCIS or invasive cancer; however, in certain cases, close observation with follow-up may be appropriate. Additionally, women who have certain high-risk lesions such as lobular carcinoma in situ, atypical ductal hyperplasia, or atypical lobular hyperplasia are at an increased risk for the future development of breast cancer and should undergo risk assessment and discussion of risk reduction measures. Ongoing and future prospective trials may provide data to better guide these management decisions and optimize patient care.

Keywords Atypical ductal hyperplasia (ADH) · Atypical lobular neoplasia (ALH) · Lobular carcinoma in situ (LCIS) · Flat epithelial atypia (FEA) · Complex sclerosing lesion · Papilloma

Introduction

Clinical management of high-risk breast lesions identified and determined to be concordant after image-guided core needle biopsy is variable and often debated. Management can include excisional biopsy to exclude upstaging to ductal carcinoma in situ (DCIS) or invasive cancer, or close imaging follow-up in certain instances. In addition, the diagnosis of a high-risk breast lesion may increase the patient's risk for the development of breast cancer in the future, prompting discussion of risk factors with implementation of appropriate surveillance regimens and risk reduction methods as appropriate. The myriad of pathology in the high-risk breast lesion spectrum, the complexity of management, and the lack of prospective data-guided decision-making encourage a multidisciplinary approach with close clinical, imaging, and pathology correlation.

This article is part of the Topical collection on *Breast Imaging*.

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High-risk lesions are reportedly identified in 5–9.2% of core needle breast biopsies [1–3]. The identification of high-risk breast lesions may increase with continued imaging advances as the transition from film-screen mammography to digital mammography has increased detection rates of high-risk lesions such as atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), and lobular neoplasia (LN) threefold [4]. There is variation among pathologists regarding core needle breast biopsy diagnosis of lesions with atypia. A recent study evaluating individual pathologists' interpretations compared to expert consensus-derived reference diagnosis revealed 48% agreement for breast lesions with atypia and 84% agreement for ductal carcinoma in situ (DCIS) [5]. This study further emphasizes the importance of radiologic-pathologic correlation with additional tissue sampling when discordant. With the detection of high-risk lesions, there is opportunity to optimize screening methods and educate the patient on prevention measures; however, there is also a risk that women may undergo unnecessary surgical procedures for benign lesions. To offer the best individualized treatment, it is important for future research to identify the clinical, imaging and pathologic predictors of invasive carcinoma. We will review the management of the following high-risk breast lesions identified on core needle biopsy with the assumption that radiologic-pathologic correlation is concordant: ADH, LN, FEA, radial scars/complex sclerosing lesions, and papillomas.

Atypical Ductal Hyperplasia (ADH) and Lobular Neoplasia

Atypical Ductal Hyperplasia

ADH resembles low-grade DCIS microscopically with atypical epithelial cells partially or completely filling less than two duct spaces or occupying less than 2 mm in maximum dimension [6]. ADH is considered a non-obligate precursor to breast cancer; however, common cytogenetic alterations including losses of 16q and 17p exist among ADH, DCIS, and invasive cancer [7]. ADH is identified in approximately 3–4% of core needle biopsies [8].

The upgrade rate for ADH identified on core needle biopsy following excision ranges from 0 to 56% [8–27, 28•, 29–31]. When reviewing studies that included greater than 100 excisional biopsies, the upgrade rate ranges from 13 to 51% [8, 12, 13, 16, 19, 21–24, 26, 27, 28•, 29, 31]. A recent large retrospective study with literature review reported an average upgrade rate for ADH of 23%. [28•]. Given the rates of upgrade at excisional biopsy as well as the quantitative nature of the pathologic diagnosis of ADH versus DCIS, excisional biopsy is recommended when ADH is identified on core needle biopsy to ensure appropriate tissue sampling and to exclude in situ or invasive cancer and is supported by the National Comprehensive Cancer Network guidelines [32]. When excisional biopsy is not performed, close imaging follow-up should be pursued.

Several studies have shown that a diagnosis of ADH increases the patient's relative risk for the future development of breast cancer ranging from 3.1 to 4.7 and this risk is for either breast [33–35]. One study reported the risk of breast cancer was 21% at 20 years for women with atypical hyperplasia and risk was related to number of foci of atypia present [34].

Lobular Neoplasia: Atypical Lobular Hyperplasia & Lobular Carcinoma in Situ

Lobular neoplasia (LN) describes a spectrum of lesions that includes atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). Lobular neoplasia is considered a non-obligate precursor for the subsequent development of invasive breast cancer. In lobular neoplasia, a monotonous population of neoplastic cells expand and replace the normal epithelial cells of the acini and intralobular ductules expanding the lobular units [36]. The differentiation between ALH and LCIS is quantitative. More than 50% of the acini of a lobular unit must be distended by neoplastic cells for a diagnosis of LCIS, and distension of less than 50% of the acini of a lobular unit would be designated ALH [37]. Pleomorphic LCIS exhibits cells with a greater degree of nuclear pleomorphism and abundant cytoplasm. Lobular neoplasia can be bilateral and multicentric [38] and most often arises in women 40–50 years of age [36]. ALH, LCIS, and invasive lobular carcinoma have been shown to have loss of heterozygosity and mutations in CDH1, the gene encoding E-cadherin [39].

Multiple retrospective studies evaluating excisional biopsy of ALH have reported upgrade rates ranging from 0 to 67% [10, 12, 28•, 40–51] with a reported average rate of 9% [28•]. Upgrade rates from LCIS to DCIS or invasive carcinoma range from 0 to 60% [10, 12, 28•, 40, 43–48, 50–53] with a reported average of 18% [28•]. Practices vary regarding excisional biopsy after LN diagnosis with imaging concordance. The National Comprehensive Cancer Network supports excisional biopsy of ALH or LCIS diagnosed by core needle biopsy when pleomorphic LCIS is present and when there is multifocal or extensive LCIS involving more than 4 terminal duct lobular units, as this has been shown to have an increased risk for invasive cancer at surgical biopsy [32, 48]. Those patients with LN and concordant imaging who do not

undergo excisional biopsy are recommended by the NCCN to have a physical exam with mammography with or without ultrasound every 6–12 months for 1 year [32].

Several studies have shown that a diagnosis of ALH increases the relative risk of breast cancer development 3.1–5.9-fold [33–35]. Studies have shown a greater increased risk for the future development of breast cancer in women diagnosed with LCIS 6.9–11.0 [54, 55].

Given the increased rates of future breast cancer development in women with ADH, ALH, and LCIS, once an associated malignancy has been excluded, women should be counseled regarding their increased risk for the development of breast cancer and undergo a risk assessment. Women who are determined to have a familial risk for breast cancer should be referred to a genetic professional. Risk reduction strategies should be discussed and may include but are not limited to lifestyle interventions, active surveillance, chemoprevention, and prophylactic mastectomy.

Lifestyle interventions include exercise, maintaining an ideal body mass index, and lowering the use of alcohol. The direct results of these measures on lowering risk for women with atypia have not been evaluated. Active surveillance includes clinical exam and history every 6–12 months and screening mammography with consideration of tomosynthesis to begin upon diagnosis of ADH or LN, but not prior to 30 years of age. A study comparing patients with a diagnosis of ADH, ALH, or LCIS to matched controls revealed no difference in the sensitivity of mammography but showed a lower specificity in the high-risk group [56]. While the role of breast MRI in patients with atypia needs further exploration, patients should undergo risk assessment as the American Cancer Society screening guidelines recommend breast MRI in women with a 20–25% lifetime risk for the development of breast cancer based on family history models, but report there is insufficient evidence to recommend for or against breast MRI in women with atypia or LCIS [57]. Physical exam is recommended by the National Comprehensive Cancer Network every 6–12 months and this is supported by a study in which 13 of 104 reported cancers were detected on physical exam [57].

Chemoprevention has been shown to reduce breast cancer incidence in women with atypical hyperplasia. The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study revealed an 86% reduction in breast cancer incidence in women with atypical hyperplasia after 5 years of therapy with Tamoxifen [58]. Additionally, the Study of Tamoxifen and Raloxifene (STAR) trial showed that raloxifene had similar risk reduction to tamoxifen with decreased toxicity in post-menopausal high-risk women [59]. Women with a diagnosis of LCIS were also represented in the aforementioned trials representing 6% of women in the NSABP P-1 trial and 9% of women in the STAR trial with a greater than 50% risk reduction for both trials in this subset of participants [58, 59]. The use of chemoprevention measures has been reported to lower the breast cancer incidence in women with a diagnosis of atypical hyperplasia and LCIS from 21 to 7.5% at 10 years [60].

Bilateral prophylactic mastectomy is the most-effective method of breast cancer risk reduction and studies suggest a 95% reduction in the risk of breast cancer in women who undergo this procedure [61]. In the absence of additional risk factors, prophylactic mastectomy is rare in women with LCIS or atypia, and a study of a cohort of participants with LCIS only 5% selected this procedure [62].

FEA

FEA is a columnar cell lesion with low-grade cytologic nuclear atypia involving the terminal duct lobular unit without architectural features of ADH or DCIS [63]. The frequent co-existence of columnar cell lesions, including FEA, LCIS, and tubular carcinoma has been termed the "Rosen Triad" prompting close surveillance at biopsy for histologic evidence of the other two entities [64].

Flat epithelial atypia is a rare lesion reported on 1.3% of breast biopsies [28•]. A recent meta-analysis identified 32 studies revealing a range in upgrade rates from 0-42% with an average upgrade rate of 11% [65•]. Studies have shown residual calcifications after core biopsy have been associated with upgrade rate [28•]. The World Health Organization suggests that surveillance may be appropriate for pure FEA in the absence of residual calcifications and presence of pathologic-radiologic concordance [63]. Currently, the Translational Breast Cancer Research Consortium (TBCRC) has a prospective trial evaluating the incidence of adjacent synchronous ipsilateral invasive carcinoma or DCIS in patients diagnosed with FEA by core needle biopsy.

The Nashville Cohort Study evaluated the long-term risk of breast cancer in patients with FEA and showed a similar relative risk for women with columnar cell lesions without atypia and FEA of 1.5 [66]. The Mayo Clinic Cohort study also showed that women with a diagnosis of FEA alone had a similar risk to women with proliferative lesions without atypia [67].

Radial Scar/Complex Sclerosing Lesion

A radial scar is a composed of proliferating tubules radiating from a central fibroelastotic core, and this term is reserved for lesions less than 1 cm. A complex sclerosing lesion is a larger (> 1 cm) radial sclerosing lesion with more complex epithelial elements. Additional proliferative

lesions are frequently associated with these lesions and include papillomas, sclerosing adenosis, and usual ductal hyperplasia.

Radial scars have been reported in 1–2% of core needle biopsies [68, 69]. A recent meta-analysis including 20 studies revealed an upgrade rate of 26% for radial scars with atypia and an upgrade rate of 7.5% for radial scars without atypia at excisional biopsy [69]. Incidental radial scars less than 5 mm have been shown to be less likely to be upgraded at excision [69] suggesting a role for imaging follow-up in these patients.

Papilloma

Solitary intraductal papillomas are intraductal growths of arborizing epithelia with fibrovascular stalks. These lesions may be associated with proliferative change or atypia. Central papillomas arise in a large duct and can be associated with clear or bloody nipple discharge. Peripheral papillomas arise in the small ducts and are more often clinically occult and identified on breast imaging.

A recent meta-analysis of 34 studies reported an upgrade rate of 15.7% to DCIS or invasive cancer following excisional biopsy for a papillary lesion identified on core biopsy [70]. The meta-analysis also showed a higher upgrade rate for atypical papillary lesion (36.9%) as compared to benign papillomas (7.0%) [70]. Several studies have reported upgrade rates from 2.3 to 2.7% associated with benign papillomas identified at core needle biopsy [71•, 72]. These studies suggest that close imaging surveillance may be appropriate in patients with a benign papilloma diagnosed at core needle biopsy with radiologic-pathologic concordance and minimal residual mass after core biopsy. Several factors have been associated with upgrade to malignancy at excisional biopsy after core needle biopsy for benign papillary lesions and include the following: $>$ 54 years of age, lesions greater than 1 cm, and patients with ipsilateral breast cancer [73]. Papillary lesions with atypia as previously mentioned have a higher rate of upgrade to malignancy and should undergo surgical excision to exclude a higher-grade lesion. Currently, the TBCRC is evaluating the incidence of adjacent synchronous ipsilateral invasive carcinoma or DCIS in patients with intraductal papilloma without atypia on core needle biopsy in a prospective trial. Benign papillary lesions confer a similar risk for the future development of breast cancer as other proliferative lesions approximately 2-fold [74–77].

Conclusions

Clinical management of high-risk breast lesions identified and determined to be concordant after image-guided core needle biopsy varies and prospective data are needed to better guide management decisions. High-risk breast lesions including ADH, LCIS, ALH FEA, radial scar, and papillary lesions require close radiologic-pathologic correlation when diagnosed by image-guided breast core needle biopsy. Excisional biopsy can exclude a higher-grade lesion such as DCIS or invasive cancer; however, in certain cases, close observation with follow-up may be appropriate. Additionally, women who have LCIS, ADH, or ALH are at an increased risk for the future development of breast cancer and should undergo risk assessment and discussion of risk reduction measures. Ongoing and future prospective trials may provide data to better guide these management decisions and optimize patient care.

Compliance with Ethical Standards

Conflict of interest Monali Lipman, Ambley Chambers, and Heidi R. Umphrey each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. El-Sayed ME, Rakha EA, Reed J, et al. Predictive value of needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening. Histopathology. 2008;53:650–7. https://doi.org/10.1111/j.1365-2559.2008.03158.x.
2. Andreu FJ, Saez A, Sentis M, et al. Breast core biopsy reporting categories–an internal validation in a series of 3054 consecutive lesions. Breast. 2007;16:94–101. https://doi.org/10.1016/j.breast.2006.06.009.
3. Houssami N, Ciatto S, Bilous M, et al. Borderline breast core needle histology: predictive values for malignancy in lesions of uncertain malignant potential (B3). Br J Cancer. 2007;96:1253–7. https://doi.org/10.1038/sj.bjc.6603714.
4. Neal CH, Coletti MC, Joe A, et al. Does digital mammography increase detection of high-risk breast lesions presenting as calcifications? AJR. 2013;201:1148–54. https://doi.org/10.2214/AJR.12.10195.
5. Elmore JG, Longton GM, Carney PA, et al. Diagnostic concordance among pathologists interpreting breast biopsy specimens. JAMA. 2015;313:1122–32. https://doi.org/10.1001/jama.2015.1405.
6. Simpson JF, Schnitt SJ, Visscher DW, et al. Atypical ductal hyperplasia. In: Lakhani SR, Ellis IO, Schnitt SJ, et al., editors.

WHO classification of tumours of the breast. Lyon: IARC; 2012. p. 88–9.
7. Lakhani SR, Collins N, Stratton MR, et al. Atypical ductal hyperplasia of the breast: clonal proliferation with loss of heterozygosity on chromosomes 16q and 17p. J Clin Pathol. 1995;48:611–5.
8. Menes TS, Rosenberg R, Balch S, et al. Upgrade of high-risk breast lesions detected on mammography in the Breast Cancer Surveillance Consortium. Am J Surg. 2014;207:24–31. https://doi.org/10.1016/j.amjsurg.2013.05.014.
9. Burbank F. Stereotactic breast biopsy of atypical ductal hyperplasia and ductal carcinoma in situ lesions: improved accuracy with directional, vacuum-assisted biopsy. Radiology. 1997;202:843–7. https://doi.org/10.1148/radiology.202.3.9051043.
10. Liberman L, Dershaw DD, Glassman JR, et al. Analysis of cancers not diagnosed at stereotactic core breast biopsy. Radiology 1997;203:151–7. 54%adhupstage.
11. Mesurolle B, Perez JC, Azzumea F, et al. Atypical ductal hyperplasia diagnosed at sonographically guided core needle biopsy: frequency, final surgical outcome, and factors associated with underestimation. AJR Am J Roentgenol. 2014;202:1389–94. https://doi.org/10.2214/AJR.13.10864.
12. Rakha EA, Lee AH, Jenkins JA, et al. Characterization and outcome of breast needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening. Int J Cancer. 2011;129:1417–24. https://doi.org/10.1002/ijc.25801.
13. Saladin C, Haueisen H, Kampmann G, et al. Lesions with unclear malignant potential (B3) after minimally invasive breast biopsy: evaluation of vacuum biopsies performed in Switzerland and recommended further management. Acta Radiol. 2016;57:815–21. https://doi.org/10.1177/0284185115610931.
14. Allison KH, Eby PR, Kohr J, et al. Atypical ductal hyperplasia on vacuum-assisted breast biopsy: suspicion for ductal carcinoma in situ can stratify patients at high risk for upgrade. Hum Pathol. 2011;42:41–50. https://doi.org/10.1016/j.humpath.2010.06.011.
15. Arpino G, Allred DC, Mohsin SK, et al. Lobular neoplasia on core-needle biopsy–clinical significance. Cancer. 2004;101:242–50. https://doi.org/10.1002/cncr.20318.
16. Bianchi S, Bendinelli B, Castellano I, et al. Morphological parameters of flat epithelial atypia (FEA) in stereotactic vacuum-assisted needle core biopsies do not predict the presence of malignancy on subsequent surgical excision. Virchows Arch. 2012;461:405–17. https://doi.org/10.1007/s00428-012-1279-y.
17. Brem RF, Behrndt VS, Sanow L, et al. Atypical ductal hyperplasia: histologic underestimation of carcinoma in tissue harvested from impalpable breast lesions using 11-gauge stereotactically guided directional vacuum-assisted biopsy. AJR Am J Roentgenol. 1999;172:1405–7. https://doi.org/10.2214/ajr.172.5.10227526.
18. Doren E, Hulvat M, Norton J, et al. Predicting cancer on excision of atypical ductal hyperplasia. Am J Surg. 2008;195:358–61. https://doi.org/10.1016/j.amjsurg.2007.11.008.
19. Eby PR, Ochsner JE, DeMartini WB, et al. Is surgical excision necessary for focal atypical ductal hyperplasia found at stereotactic vacuum-assisted breast biopsy? Ann Surg Oncol. 2008;15:3232–8. https://doi.org/10.1245/s10434-008-0100-2.
20. Ely KA, Carter BA, Jensen RA, et al. Core biopsy of the breast with atypical ductal hyperplasia: a probabilistic approach to reporting. Am J Surg Pathol. 2001;25:1017–21.
21. Forgeard C, Benchaib M, Guerin N, et al. Is surgical biopsy mandatory in case of atypical ductal hyperplasia on 11-gauge core needle biopsy? A retrospective study of 300 patients. Am J Surg. 2008;196:339–45. https://doi.org/10.1016/j.amjsurg.2007.07.038.
22. Khoury T, Chen X, Wang D, et al. Nomogram to predict the likelihood of upgrade of atypical ductal hyperplasia diagnosed on a core needle biopsy in mammographically detected lesions. Histopathology. 2015;67:106–20. https://doi.org/10.1111/his.12635.
23. Khoury T, Li Z, Sanati S, et al. The risk of upgrade for atypical ductal hyperplasia detected on magnetic resonance imaging-guided biopsy: a study of 100 cases from four academic institutions. Histopathology. 2016;68:713–21. https://doi.org/10.1111/his.12811.
24. Kohr JR, Eby PR, Allison KH, et al. Risk of upgrade of atypical ductal hyperplasia after stereotactic breast biopsy: effects of number of foci and complete removal of calcifications. Radiology. 2010;255:723–30. https://doi.org/10.1148/radiol.09091406.
25. Lourenco AP, Khalil H, Sanford M, et al. High-risk lesions at MRI-guided breast biopsy: frequency and rate of underestimation. AJR Am J Roentgenol. 2014;203:682–6. https://doi.org/10.2214/AJR.13.11905.
26. McGhan LJ, Pockaj BA, Wasif N, et al. Atypical ductal hyperplasia on core biopsy: an automatic trigger for excisional biopsy? Ann Surg Oncol. 2012;19:3264–9. https://doi.org/10.1245/s10434-012-2575-0.
27. McLaughlin CT, Neal CH, Helvie MA. Is the upgrade rate of atypical ductal hyperplasia diagnosed by core needle biopsy of calcifications different for digital and film-screen mammography? AJR Am J Roentgenol. 2014;203:917–22. https://doi.org/10.2214/AJR.13.11862.
28. • Mooney KL, Bassett LW, and Apple SK. Upgrade rates of high-risk breast lesions diagnosed on core needle biopsy: a single institution experience and literature review. Modern Pathology 2016;29:1471–84. https://doi.org/10.1038/modpathol.2016.127. This is a large retrospective analysis of high-risk breast lesions with a large review of the literature. This paper summarizes upgrade rates for many high-risk lesions.
29. Nguyen CV, Albarracin CT, Whitman GJ, et al. Atypical ductal hyperplasia in directional vacuum- assisted biopsy of breast microcalcifications: considerations for surgical excision. Ann Surg Oncol. 2011;18:752–61. https://doi.org/10.1245/s10434-010-1127-8.
30. Sohn V, Arthurs Z, Herbert G, et al. Atypical ductal hyperplasia: improved accuracy with the 11- gauge vacuum-assisted versus the 14-gauge core biopsy needle. Ann Surg Oncol. 2007;14:2497–501. https://doi.org/10.1245/s10434-007-9454-0.
31. Wagoner MJ, Laronga C, Acs G. Extent and histologic pattern of atypical ductal hyperplasia present on core needle biopsy specimens of the breast can predict ductal carcinoma in situ in subsequent excision. Am J Clin Pathol. 2009;131:112–21. https://doi.org/10.1309/AJCPGHEJ2R8UYFGP.
32. National Comprehensive Cancer Network (NCCN). https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. Accessed 24 Nov 2017.
33. Page DL, Dupont WD, Rogers LW, et al. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer. 1985;55:2698–708.
34. Collins LC, Baer HJ, Tamimi RM, et al. Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. Cancer. 2007;109:180–7. https://doi.org/10.1002/cncr.22408.
35. Degnim AC, Visscher DW, Berman HK, et al. Stratification of breast cancer risk in women with atypia: a Mayo cohort study. J Clin Oncol. 2007;25:2671–7. https://doi.org/10.1200/JCO.2006.09.0217.
36. Rosen PP, Kosloff C, Leiberman PH, et al. Lobular carcinoma in situ of the breast. Detailed analysis of 99 patients with average follow-up of 24 years. Am J Surg Pathol. 1978;2:225–51.
37. Page DL, Kidd TE Jr, Dupont WD, et al. Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. Hum Pathol. 1991;22:1232–9.

38. Beute BJ, Kalisher L, Hutter RV. Lobular carcinoma in situ of the breast: clinical, pathologic, and mammographic features. AJR Am J Roentgenol. 1991;157:257–65. https://doi.org/10.2214/ajr.157.2.1853802.
39. Mastracci TL, Tjan S, Bane AL, et al. E-cadherin alterations in atypical lobular hyperplasia and lobular carcinoma in situ of the breast. Mod Pathol. 2005;18:741–51. https://doi.org/10.1038/modpathol.3800362.
40. Londero V, Zuiani C, Linda A, et al. Lobular neoplasia: core needle breast biopsy underestimation of malignancy in relation to radiologic and pathologic features. Breast. 2008;17:623–30. https://doi.org/10.1016/j.breast.2008.05.007.
41. Middleton LP, Grant S, Stephens T, et al. Lobular carcinoma in situ diagnosed by core needle biopsy: when should it be excised? Mod Pathol. 2003;16:120–9. https://doi.org/10.1097/01.MP.0000051930.68104.92.
42. Allen S, Levine EA, Lesko N, et al. Is excisional biopsy and chemoprevention warranted in patients with atypical lobular hyperplasia on core biopsy? Am Surg. 2015;81:876–8.
43. Brem RF, Lechner MC, Jackman RJ, et al. Lobular neoplasia at percutaneous breast biopsy: variables associated with carcinoma at surgical excision. AJR Am J Roentgenol. 2008;190:637–41. https://doi.org/10.2214/AJR.07.2768.
44. Elsheikh TM, Silverman JF. Follow-up surgical excision is indicated when breast core needle biopsies show atypical lobular hyperplasia or lobular carcinoma in situ: a correlative study of 33 patients with review of the literature. Am J Surg Pathol. 2005;29:534–43.
45. Heller SL, Elias K, Gupta A, et al. Outcome of high-risk lesions at MRI-guided 9-gauge vacuum- assisted breast biopsy. AJR Am J Roentgenol. 2014;202:237–45. https://doi.org/10.2214/AJR.13.10600.
46. Ibrahim N, Bessissow A, Lalonde L, et al. Surgical outcome of biopsy-proven lobular neoplasia: is there any difference between lobular carcinoma in situ and atypical lobular hyperplasia? AJR Am J Roentgenol. 2012;198:288–91. https://doi.org/10.2214/AJR.11.7212.
47. Niell B, Specht M, Gerade B, et al. Is excisional biopsy required after a breast core biopsy yields lobular neoplasia? AJR Am J Roentgenol. 2012;199:929–35. https://doi.org/10.2214/AJR.11.8447.
48. Rendi MH, Dintzis SM, Lehman CD, et al. Lobular in- situ neoplasia on breast core needle biopsy: imaging indication and pathologic extent can identify which patients require excisional biopsy. Ann Surg Oncol. 2012;19:914–21. https://doi.org/10.1245/s10434-011-2034-3.
49. Shah-Khan MG, Geiger XJ, Reynolds C, et al. Long- term follow-up of lobular neoplasia (atypical lobular hyperplasia/lobular carcinoma in situ) diagnosed on core needle biopsy. Ann Surg Oncol. 2012;19:3131–8. https://doi.org/10.1245/s10434-012-2534-9.
50. Subhawong AP, Subhawong TK, Khouri N, et al. Incidental minimal atypical lobular hyperplasia on core needle biopsy: correlation with findings on follow-up excision. Am J Surg Pathol. 2010;34:822–8. https://doi.org/10.1097/PAS.0b013e3181dd8516.
51. Zhao C, Desouki MM, Florea A, et al. Pathologic findings of follow-up surgical excision for lobular neoplasia on breast core biopsy performed for calcification. Am J Clin Pathol. 2012;138:72–8. https://doi.org/10.1309/AJCPYG48TUTFIBMR.
52. D'Alfonso TM, Wang K, Chiu YL, et al. Pathologic upgrade rates on subsequent excision when lobular carcinoma in situ is the primary diagnosis in the needle core biopsy with special attention to the radiographic target. Arch Pathol Lab Med. 2013;137:927–35. https://doi.org/10.5858/arpa.2012-0297-OA.
53. Destounis SV, Murphy PF, Seifert PJ, et al. Management of patients diagnosed with lobular carcinoma in situ at needle core biopsy at a community-based outpatient facility. AJR Am J Roentgenol. 2012;198:281–7. https://doi.org/10.2214/AJR.11.7043.
54. Haagensen CD, Lane N, Lattes R, et al. Lobular neoplasia (so called lobular carcinoma in situ) of the breast. Cancer. 1978;42:737–69.
55. Ottesen GL, Graversen HP, Blichert-Toft M, et al. Lobular carcinoma in situ of the female breast. Short-term results of a prospective nationwide study. The Danish Breast Cancer Cooperative Group. Am J Surg Pathol. 1993;17:14–21.
56. Houssami N, Abraham LA, Onega T, et al. Accuracy of screening mammography in women with a history of lobular carcinoma in situ or atypical hyperplasia of the breast. Breast Cancer Res Treat. 2014;145:765–73. https://doi.org/10.1007/s10549-014-2965-z.
57. King TA, et al. Is there a role for routine screening MRI in women with LCIS? Breast Cancer Res Treat. 2013;142:445–53. https://doi.org/10.1007/s10549-013-2725-5.
58. Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90:1371–88.
59. Vogel VG, Constantino JP, Wickerman DL, et al. Effects of tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295:2727–41. https://doi.org/10.1001/jama.295.23.joc60074.
60. Coopey SB, Mazzola E, Buckley JM, et al. The role of chemoprevention in modifying the risk of breast cancer in women with atypical breast lesions. Breast Cancer Res Treat. 2012;136:627–33. https://doi.org/10.1007/s10549-012-2318-8.
61. Geiger AM, Yu O, Herrinton LJ, et al. A population-based study of bilateral prophylactic mastectomy efficacy in women at elevated risk for breast cancer in community practices. Arch Intern Med. 2005;165:516–20. https://doi.org/10.1001/archinte.165.5.516.
62. Oppong BA, King TA. Recommendations for women with lobular carcinoma in situ (LCIS). Oncology. 2011;25:1051–6.
63. Schnitt SJ, Collins LC, Lakhani SR, et al. Flat epithelial atypia. In: Lakhani SR, Ellis IO, Schnitt SJ, et al., editors. WHO classification of tumors of the breast. Lyon: International Agency for Research on Cancer; 2013. p. 87.
64. Brandt SM, Young GQ, Hoda SA. The "Rosen Triad": tubular carcinoma, lobular carcinoma in situ, and columnar cell lesions. Adv Anat Pathol. 2008;15:140–6. https://doi.org/10.1097/PAP.0b013e31816ff313.
65. • Rudin AV, Hoskin TL, Fahy A et al. Flat epithelial atypia on core biopsy and upgrade to cancer: a systematic review and meta-analysis. Ann Surg Oncol 2017; https://doi.org/10.1245/s10434-017-6059-0. This manuscript is a systematic review and meta-analysis for flat epithelial atypia identified at core biopsy and its upgrade rate at excisional biopsy.
66. Boulos FI, Dupont WD, Simpson JF, et al. Histologic associations and long-term cancer risk in columnar cell lesions of the breast: a retrospective cohort and a nested case-control study. Cancer. 2008;113:2415–21. https://doi.org/10.1002/cncr.23873.
67. Said SM, Visscher DW, Nassar A, et al. Flat epithelial atypia and risk of breast cancer: a Mayo cohort study. Cancer. 2015;121:1548–55. https://doi.org/10.1002/cncr.29243.
68. Miller CL, West JA, Bettini AC, et al. Surgical excision of radial scars diagnosed by core biopsy may help predict future risk of breast cancer. Breast Cancer Res Treat. 2014;145:331–8. https://doi.org/10.1007/s10549-014-2958-y.

69. Conlon N, D'Arcy C, Kaplan JB, et al. Radial scar at image-guided needle biopsy: is excision necessary? Am J Surg Pathol. 2015;39:779–85. https://doi.org/10.1097/PAS.0000000000000393.
70. Wen X, Chen W. Nonmalignant breast papillary lesions at core-needle biopsy: a meta-analysis of underestimation and influencing factors. Ann Surg Oncol. 2013;20:94–101. https://doi.org/10.1245/s10434-012-2590-1.
71. • Pareja F, Corben AD, Brennan SB et al. Breast intraductal papillomas without atypia in radiologic-pathologic concordant core-needle biopsies: rate of upgrade to carcinoma at excision. Cancer 2016;122:2819–27. https://doi.org/10.1002/cncr.30118. This is a large retrospective review evaluating upgrade rate for intraductal papillomas without atypia identified at core needle biopsy with attention to radiologic-pathology concordance and exclusion of discordant cases from analysis.
72. Tatarian T, Sokas C, Rufail M, et al. Intraductal papilloma with benign pathology on breast core biopsy: to excise or not? Ann Surg Oncol. 2016;23:2501–7. https://doi.org/10.1245/s10434-016-5182-7.
73. Hong YR, Song BJ, Jung SS, et al. Predictive factors for upgrading patients with benign breast papillary lesions using a core needle biopsy. J Breast Cancer. 2016;19:410–6. https://doi.org/10.4048/jbc.2016.19.4.410.
74. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med. 1985;312:146–51. https://doi.org/10.1056/NEJM198501173120303.
75. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005;353:229–37. https://doi.org/10.1056/NEJMoa044383.
76. Carter CL, Corle DK, Micozzi MS, et al. A prospective study of the development of breast cancer in 16,692 women with benign breast disease. Am J Epidemiol. 1988;128:467–77.
77. London SJ, Connolly JL, Schnitt SJ, et al. A prospective study of benign breast disease and the risk of breast cancer. JAMA. 1992;267:941–4.