

Atypical Hyperplasia Found Incidentally during Routine Breast Reduction Mammoplasty: Incidence and Management

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Background: Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) of the breast are premalignant lesions. Although the literature on ADH and ALH as a whole is well-developed, research on ADH and ALH incidentally discovered during breast reduction is less robust.

Methods: In this study, 355 patients undergoing bilateral reduction mammoplasty at West Virginia University were retrospectively reviewed. A variety of demographic and clinicopathologic variables were collected for each patient, and the incidence of atypical hyperplasia was calculated. Four patients (1.13%) were found to have atypical hyperplasia, three ALH, and one ADH, which is within the range reported in the literature. For patients incidentally found to have atypical hyperplasia, an in-depth analysis of postoperative management was performed.

Results: Of the four patients with atypical hyperplasia, three were referred to a cancer center, and one patient followed only with plastic surgery. The three patients who were referred to a cancer center saw a breast surgeon, whereas the patient followed only by plastic surgery did not. None of the four patients received anti-estrogen therapy, but each patient who followed with a cancer center was offered treatment and declined.

Conclusions: As a relatively uncommon finding with complex management guidelines, atypical hyperplasia discovered on breast reduction should be referred to a cancer center for long-term follow-up and management when possible. Further research is needed to assess if the management of atypical hyperplasia discovered incidentally after routine reduction should mimic treatment of atypical hyperplasia found after biopsy for suspicion of malignancy. (*Plast Reconstr Surg Glob Open* 2022;10:e4141; doi: 10.1097/GOX.0000000000004141; Published online 22 February 2022.)

INTRODUCTION

Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) are collectively known as atypical hyperplasia of the breast. Atypical hyperplasia of the breast is distinguished from ductal carcinoma in situ and lobular carcinoma in situ based on qualitative factors such as degree of hyperplasia and atypia, and quantitative

factors such as lesion size.¹ ALH is a neoplastic proliferation of epithelial cells originating in the terminal duct lobular unit. Cells are dyscohesive and monomorphic. By definition, there is expansion of less than 50% of the acini in a terminal duct lobular unit, whereas greater than 50% involvement constitutes lobular carcinoma in situ.² The growth pattern is due to impaired e-cadherin function, and thus, ALH and other lobular neoplasias are negative for e-cadherin on immunostains. Historically there has been some debate over the implications of ALH; it has been considered at times a risk indicator, and more recently, a nonobligate precursor. ALH is a marker of increased constitutional breast cancer risk, with an elevated risk for subsequent cancers of different histologic types bilaterally (with an ipsilateral predominance). ADH is an epithelial proliferation with morphologic features similar to those seen in low-grade ductal carcinoma in situ but insufficient by either qualitative or quantitative measures. It is

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considered a very early neoplastic step in the pathway to low-grade DCIS and ER-positive, low-grade invasive ductal carcinoma.² ADH and ALH have serious implications for patient management due to an approximately four to five times increase in lifetime risk for the development of invasive breast cancer.^{3–5}

In women who have ADH or ALH discovered on biopsy after imaging, 25-year incidence of carcinoma is approximately 25%–30%, a significant increase from the roughly one in eight (12.5%) women in the United States that develop breast cancer in their lifetime.^{6,7} Current management of atypical hyperplasia of the breast is variable based on patient preferences and clinical factors. Historically, treatment has involved surgical resection to mitigate long-term risk, particularly in the treatment of ADH.⁸ Yet, recent studies have shown uncertain risk in the short-term. For example, progression from atypical hyperplasia to invasive carcinoma was found to be nearly 10% after 7 years in one recent study, but only 5% after 10 years in the Breast Cancer Surveillance Consortium study, the largest of its kind to date.^{9,10} In addition, many breast cancers that arise in the setting of atypical hyperplasia are low-grade, Stage 1, ER+ carcinomas that represent relatively low-mortality malignancies that respond well to current surgical and medical therapies.⁹ Thus, close monitoring and anti-estrogen regimens, in the absence of prophylactic surgical excision, may have a role in the management, especially in populations with favorable exogenous risk factors.

According to the American Society of Plastic Surgeons, 101,126 women underwent reduction mammoplasty in 2018 in the United States: 57% for medical reasons, and 43% for cosmetic reasons.¹¹ Studies examining the incidence of atypical hyperplasia discovered during routine bilateral breast reduction are few, and the results are varied, with reported incidence ranging from 0.45% to 9.3%.^{12–16} Furthermore, when atypical hyperplasia is discovered in the setting of reduction mammoplasty, it is not always clear how the patient should be managed, as research is limited. Most studies detailing the management of patients with ADH and ALH have been in the setting of diagnosis after suspicious mammogram or other imaging, not after incidental finding on breast reduction.

The primary goals of this study are to determine the incidence of atypical hyperplasia found incidentally during bilateral breast reduction mammoplasty at West Virginia University (WVU) between 2010 and 2020 and to assess the management strategy for such patients after discovery of atypical hyperplasia at our institution.

METHODS

This study was approved by the institutional review board at WVU. A retrospective review of the medical records of all women undergoing bilateral reduction mammoplasty at WVU between 2010 and 2020 was conducted. Patients with a personal history of invasive carcinoma of the breast or carcinoma in situ of the breast before reduction were excluded from the study. Patients under the age of 18 years at the time of reduction were

Takeaways

Question: What is the incidence of atypical hyperplasia in routine reduction mammoplasty, and how should such patients be managed?

Findings: Three-hundred-and-fifty-five patients underwent bilateral reduction. Four patients (1.13%) were found to have atypical hyperplasia on pathological analysis, consistent with reported incidence in the literature. Patients referred to a cancer center were seen by a breast surgeon, offered anti-estrogen therapy, and were less likely to be lost to follow-up.

Meaning: As an uncommon finding with complex management guidelines, atypical hyperplasia discovered on breast reduction should be referred to a cancer center for long-term management.

also excluded, and 355 women were ultimately identified as the subjects of this study.

For these patients, a variety of demographic variables were collected, including race, age, driving time to surgery, body mass index, history of diabetes mellitus, alcohol use, and tobacco use. Date of surgery, date of preoperative mammogram, and date of last follow-up were also recorded. Preoperative mammogram was defined as a bilateral screening or diagnostic mammogram performed before bilateral reduction. Date of last follow-up was defined as the most recent date a patient was seen in clinic by a member of the WVU plastic surgery department. Additional variables were collected to assess baseline breast cancer risk, including estrogen exposure (supplemental estrogen use, number of children, breastfeeding history) and family history of breast and ovarian cancer.

Information specific to the breast reductions performed was also collected, including incidence of atypical hyperplasia, weight of breast tissue removed for each breast (grams), and volume of breast tissue removed for each breast (cm³). Density of the tissue removed from each breast (g/cm³) was calculated from weight and volume.

The pathology protocol for grossing and processing reduction mammoplasties at WVU is to first weigh and measure the breast tissue. The presence or absence of skin is recorded. The specimen is serially sectioned, and the percent of adipose and fibrous tissue is recorded. A linear piece of skin and three representative sections of breast tissue are submitted. If there are any grossly evident lesions, these are described and submitted for microscopic examination in addition to the usual representative sections. Tissue is fixed in formalin for 6–72 hours to meet guidelines for biomarker testing in the event carcinoma is discovered. Formalin-fixed paraffin-embedded tissue is cut, placed on glass slides, and stained with hematoxylin and eosin. All cases are reviewed and signed out by pathologists. Additional work-up is not done routinely; however, cases with suspected atypical hyperplasia on H&E were also stained with immunostains such as e-cadherin, ER, and CK5/6.

For patients with atypical hyperplasia identified at the time of breast reduction, an in-depth analysis of postoperative management was then performed. All continuous variables in this study are reported as median with interquartile range or mean with SD, as specified.

RESULTS

For the 355 women included in this study, demographic and breast cancer risk factor information is shown in Table 1. The vast majority of patients included in this study were White (97.18%), reflecting the majority White Appalachian population that is served by WVU. In addition, 1.41% of patients were Hispanic, 0.56% of patients were Black, and 0.85% of patients were of unknown background. The median age of patients in this study was 43 years (IQR 32–52.75). Average body mass index was 34.18 kg/m² (SD 7.25). Approximately 6.5% of patients had a diagnosis of either diabetes mellitus type I or type II, 35.9% of patients reported use of alcohol, and 11.4% were active smokers at the time of initial consult. It is our policy to have patients stop use of all types of nicotine at least 4 weeks before surgery.

The 355 breast reductions in this study were performed by 12 different surgeons. Reduction information is shown in Table 2. Median breast tissue weight removed on bilateral reduction was 1532 g (IQR 1067–2202), available for 349 patients. Median breast volume removed was 3469 cm³ (IQR 2451–5206), available for 328 patients. This corresponded to a median breast density of 0.42 g per cm³ (IQR 0.35–0.53) (n = 325). In this study, breast density was highest in the 30–39 age group (0.44 g/cm³), and lowest in the 60+ age group (0.38 g/cm³). A total of four patients were found to have atypical hyperplasia after reduction in this study, an incidence of 1.13%. Three of these patients were found to have ALH (0.85%), and one patient was found to have ADH (0.28%).

Detailed pathological and follow-up information for the four patients found to have atypical hyperplasia is

shown in Table 3. As shown, one patient was found to have ADH, and three patients were found to have ALH (Fig. 1). In one patient, two foci of ALH were seen, but only one focus of atypical hyperplasia was identified in the others. Follow-up times with plastic surgery were 23 months, 5 months, 4 months, and 17 months for each of the four patients. The patient that followed with plastic surgery for 23 months was not referred to a cancer center and was lost to follow-up, unlike the other three patients, who continue to follow with an oncologist. All three patients referred to a cancer center for treatment were also followed by a breast surgeon. Mammogram screening was recommended yearly for three patients and every 6 months for one patient. None of the four patients underwent anti-estrogen therapy, though each patient who was referred to a cancer center was offered treatment.

Preoperative mammography information was recorded for each of the 355 women included in this study. Table 4 shows preoperative mammography compliance with common societal guidelines, including the American Cancer Society, the United States Preventative Task Force/American Academy of Family Physicians (USPSTF/AAFP), the American College of Radiology, and the American Society of Breast Surgeons. As shown, our patients met minimum preoperative mammography recommendations between 85.6% and 97.2% of the time, depending on the stringency of the societal recommendations.

DISCUSSION

The incidence of atypical hyperplasia (ADH or ALH) found on bilateral breast reduction in this study was 1.13%, within the range reported in the literature (0.45%–9.3%).^{12–16} One likely reason that this incidence is on the lower end of the reported range is that patients with a personal history of breast carcinoma or carcinoma in situ were excluded. We elected to exclude these patients because the primary aim of this study was to characterize

Table 1. Characteristics of Women Over the Age of 18 Years without Personal History of Breast Cancer Undergoing Bilateral Breast Reduction at WVU from 2010 to 2020 (n = 355)

Demographic Information	
% Caucasian, non-Hispanic	97.18%
% Black	0.56%
% Hispanic	1.41%
% Unknown	0.85%
Median age, y (IQR)	43 (32–52.75)
Mean BMI, kg/m ² (SD)	34.18 (7.25)
<20 years of age (SD)	30.03 (5.52)
20–29 (SD)	33.61 (7.94)
30–39 (SD)	35.29 (7.18)
40–49 (SD)	34.93 (7.70)
50–59 (SD)	33.61 (6.31)
60+ (SD)	34.20 (6.96)
% Diabetes mellitus (% unknown)	6.5% (0.0%)
% Alcohol use (% unknown)	35.9% (4.2%)
% Active tobacco use (% former use; % unknown)	11.4% (20.0%; 1.1%)
Median driving time to WVU, min (IQR)	68.5 (28–130)
Breast Cancer Risk Information	
Mean number of children (SD)	1.30 (1.17) (n = 297)
% With known history of breastfeeding (% no children; % unknown)	14.7% (29.1%; 37.6%)
% Known use of supplemental estrogen (% estrogen use not documented)	25.1% (74.9%)
% Family history of breast cancer (% breast cancer in first-degree relative; % unknown)	34.5% (8.2%; 5.4%)
% Family history of ovarian cancer (% ovarian cancer in first-degree relative; % unknown)	4.8% (1.7%; 5.9%)

Table 2. Reduction Information for Women Over the Age of 18 years without Personal History of Breast Cancer Undergoing Bilateral Breast Reduction at WVU from 2010 to 2020 (n = 355)

Reduction Information	
% Atypia identified (No. cases)	1.13% (4)
% Atypical ductal hyperplasia (ADH) (No. cases)	0.28% (1)
% Atypical lobular hyperplasia (ALH) (No. cases)	0.85% (3)
Median breast tissue weight removed (g) (IQR)	1532 (1067–2202) (n = 349)
Median breast tissue volume removed (cm ³) (IQR)	3469 (2451–5206) (n = 328)
Median density of breast tissue removed (g/cm ³) (IQR)	0.42 (0.35–0.53) (n = 325)
<20 years of age (IQR)	0.42 (0.28–0.52)
20–29 (IQR)	0.41 (0.35–0.53)
30–39 (IQR)	0.44 (0.36–0.57)
40–49 (IQR)	0.42 (0.36–0.57)
50–59 (IQR)	0.40 (0.35–0.50)
60+ (IQR)	0.38 (0.32–0.50)

patients at increased risk of breast cancer after routine reduction mammoplasty. Patients with a personal history of breast cancer before breast reduction are already under close surveillance for recurrence, and thus management would not likely change after an incidental finding of atypical hyperplasia during reduction.

The major limitation of this study is the low number of patients found to have atypical hyperplasia (ADH or ALH) on routine bilateral reduction mammoplasty (n = 4). However, the low incidence at our institution is consistent with the rarity with which plastic surgeons, particularly those at smaller institutions or in community practice, may encounter ADH or ALH during routine breast reduction mammoplasty. Thus, with many plastic surgeons having limited experience with incidental diagnoses of ADH and ALH, a standardized recommendation is needed to ensure proper follow-up and to optimize patient care. In our experience, all three patients with atypical hyperplasia who were referred to a cancer center for follow-up care in this study continued annual or six-month mammogram screening. In contrast, the patient with atypical hyperplasia who was managed exclusively by her plastic surgeon was lost to follow-up. In addition, the three patients who were referred to a cancer center were also seen by a breast surgeon, whereas the patient who was managed only by her plastic surgeon was not. It is therefore our recommendation that plastic surgeons refer patients who are found to have atypical hyperplasia on routine breast reduction to a cancer center for follow-up management. Our recommendation is in congruence with the algorithm designed by Goodwin et al.¹⁵ In the case that referral to a cancer center is not possible due to geographic or other patient factors, plastic surgeons should at minimum recommend mammographic surveillance in the form of annual mammogram for patients with incidentally discovered atypical

hyperplasia, as well as discuss the potential risks and benefits of anti-estrogen therapy.

Cancer centers provide long-term multidisciplinary care from breast surgeons and oncologists trained to manage patients with precancerous lesions. Cancer center referral has also been shown to change management strategy, specifically in patients incidentally found to have atypical hyperplasia after breast reduction. A 2019 study conducted by Mastroianni et al found that, in patients diagnosed with ADH or ALH after routine breast reduction, 45% of referrals to a cancer center led to a change in treatment, often the addition of anti-estrogen therapy.¹⁴ Most commonly, tamoxifen, raloxifene, and aromatase inhibitors such as exemestane are prescribed for 5 years of chemo-preventative therapy in such patients,²² each of which require close follow-up to monitor for adverse effects. Anti-estrogen therapy has been shown to reduce the risk of breast cancer in patients with atypical hyperplasia by approximately 75%.²³ Cancer center referral also provides patients a streamlined approach to ensure adequate mammogram screening on the same day as follow-up. This is particularly valuable in a rural setting like ours, where sites performing mammograms may be a long distance away and multiple appointments may present a barrier to care.

Additionally, we believe that cancer center referral is prudent because of the complexity of management of patients with atypical hyperplasia. Conflicting treatment algorithms and changing recommendations may make management outside of the scope of practice of most plastic surgeons. Such complexity is evidenced by the lack of interdisciplinary consensus of how patients with atypical hyperplasia should be managed. For example, pathologists and radiologists tend to recommend surgical management over increased imaging surveillance,²⁴ whereas

Table 3. Pathological and Follow-up Information for the Four Patients with Identified Atypical Hyperplasia of the Breast

	No. ADH/ALH Foci Identified	Size of ADH/ALH	Developed Carcinoma	Referred to Cancer Center	Follow-up with Plastic Surgery (mo)	Mammogram Screening Frequency	Follow-up with Breast Surgeon	Anti-estrogen Therapy
Patient 1	2 foci of ALH	Not specified	No	No; followed with plastic surgery	23	Yearly	No	No
Patient 2	1 focus of ALH	2 mm	No	Yes	5	Every 6 mo	Yes	Declined
Patient 3	1 focus of ADH	Not specified	No	Yes	4	Yearly	Yes	Declined
Patient 4	1 focus of ALH	Not specified	No	Yes	17	Yearly	Yes	Declined

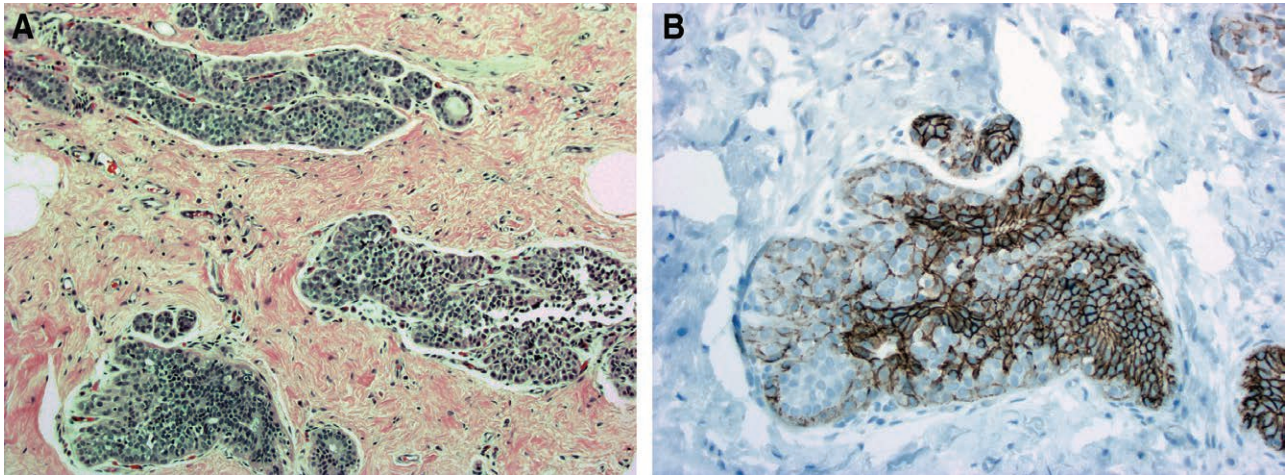


Fig. 1. A, ALH: proliferation of monomorphic cells in terminal duct lobular unit with less than half of acini expanded (H&E stain, 100x). B, ALH: E-cadherin is negative in lobular neoplasia (e-cadherin stain, 200x).

breast surgeons and oncologists tend to recommend serial imaging surveillance with anti-estrogen therapy due to an ultimately low perceived risk of malignant transformation.²⁵ Although data are limited, plastic surgeons often recommend increased imaging surveillance with or without anti-estrogen therapy.²⁶ BRCA testing and breast MRI are sometimes indicated for patients perceived to be at higher risk, including patients with strong family history of breast cancer.²⁶

Furthermore, research regarding optimal treatment of atypical hyperplasia discovered incidentally is sparse, and it is not clear if the current literature on atypical hyperplasia as a whole is readily generalizable to this population. Unlike patients who have undergone biopsy after a suspicious lesion on mammography, patients undergoing reduction mammoplasty generally have no predetermined risk of breast cancer or high-risk lesion. In this way, patients undergoing reduction mammoplasty are not preselected as a breast cancer risk and represent a distinct population from patients undergoing biopsy of the breast after suspicious mammography. In addition, patients with ADH or ALH discovered on routine breast

reduction have, in effect, undergone an excision of the lesion during reduction. There is no consensus among breast surgeons and oncologists regarding management of atypical hyperplasia discovered during reduction mammoplasty, and guidelines vary from institution to institution.²⁶ Thus, further research is important to determine the precise benefit of interventions for patients in whom atypical hyperplasia is incidentally discovered.

Societal recommendations regarding mammogram screening are varied, as shown in Table 4. Our plastic surgery division policy has been to recommend preoperative mammogram for patients over the age of 40 who have not had a mammogram in the past year, thus adhering to the strict standards set by the American Society of Breast Surgeons. It is important to note that, though recommendations have evolved over the past decade, our department policy has resulted in between 85% and 97% compliance with current mammography guidelines, depending on the societal recommendation. Patients 40 years of age and older without a documented preoperative mammography likely either (1) failed to comply with mammography recommendations or (2) obtained a mammogram at an

Table 4. Preoperative Mammography Compliance with Common Societal Guidelines, including the American Cancer Society, the United States Preventative Task Force/American Academy of Family Physicians (USPSTF/AAFP), the American College of Radiology, and the American Society of Breast Surgeons

	Recommendation Summary	Proportion Meeting Guidelines
American Cancer Society (ACS) ¹⁷	<ul style="list-style-type: none"> • Optional annual mammogram between the ages of 40 and 44 • Annual mammogram between the ages of 45 and 54 • Mammography every 2 years in women aged 55 and over 	*Including ages ≥40: 186/208 (89.4%) Including ages ≥45: 148/163 (90.8%)
United States Preventative Task Force/ American Academy of Family Physicians (USPSTF/AAFP) ^{18,19}	<ul style="list-style-type: none"> • Optional mammography every 2 years between the ages of 40 and 49 • Mammography every 2 years in women aged 50 years and over 	*Including ages ≥40–74: 194/208 (93.3%) Including ages ≥50–74: 106/109 (97.2%)
American College of Radiology (ACR) ²⁰	<ul style="list-style-type: none"> • Breast cancer risk assessment at age 30 • Annual mammogram beginning at age 40 	Including Ages ≥40: 178/208 (85.6%)
American Society of Breast Surgeons ²¹	<ul style="list-style-type: none"> • Breast cancer risk assessment at age 25 • Annual mammogram beginning at age 40 	Including Ages ≥40: 178/208 (85.6%)

outside facility that was not documented in our electronic health record. In any case, this represents an opportunity for institutional improvement, as our goal is for every patient 40 years of age and older to have preoperative mammography within one year of surgery. Preoperative mammograms before breast reduction have been shown to detect high-risk lesions in roughly 1.3% of patients and cancer in 0.3% of patients, based on a study of more than 600 patients.²⁷

CONCLUSIONS

The incidence of atypical hyperplasia found on routine bilateral breast reduction in this study (1.13%) is within with the range reported in the literature. As a relatively uncommon finding with complex management guidelines, atypical hyperplasia discovered on breast reduction should be referred to a cancer center for long-term follow-up and management. If coordination with a cancer center is precluded, surveillance with a minimum of annual mammography should be encouraged and anti-estrogen therapy should be discussed with the patient. Further research is needed to assess if the management of atypical hyperplasia discovered incidentally after routine reduction should mimic treatment of atypical hyperplasia found after biopsy for suspicion of malignancy.

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