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Association of Breast Cancer with the Finding of Atypical Ductal Hyperplasia at Core Breast Biopsy

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Objective
The purpose of the study is to evaluate the prevalence of occult breast carcinoma in surgical breast biopsies performed on nonpalpable breast lesions diagnosed initially as atypical ductal hyperplasia (ADH) by core needle biopsy.

Background
Atypical ductal hyperplasia is a lesion with significant malignant potential. Some authors note that ADH and ductal carcinoma *in situ* (DCIS) frequently coexist in the same lesion. The criterion for the diagnosis of DCIS requires involvement of at least two ducts; otherwise, a lesion that is qualitatively consistent with DCIS but quantitatively insufficient is described as atypical ductal hyperplasia. Thus, the finding of ADH in a core needle breast biopsy specimen actually may represent a sample of a true *in situ* carcinoma.

Methods
Between May 3, 1994, and June 12, 1996, image-guided core biopsies of 510 mammographically identified lesions were performed using a 14-gauge automated device with an average of 7.5 cores obtained per lesion. Atypical ductal hyperplasia was found in 23 (4.5%) of 510 lesions, and surgical excision subsequently was performed in 21 of these cases. In these 21 cases, histopathologic results from core needle and surgical biopsies were reviewed and correlated.

Results
Histopathologic study of the 21 surgically excised lesions having ADH in their core needle specimens showed seven (33.3%) with DCIS.

Conclusions
In the authors' patient population, one third of patients with ADH at core biopsy have an occult carcinoma. A core needle breast biopsy finding of ADH for nonpalpable lesions therefore warrants a recommendation for excisional biopsy.

Breast cancer is the most common nonskin cancer among women in the United States. In 1996, it is estimated that 184,300 women will be diagnosed and 44,300 will die of the disease.[1] Core needle biopsy has become the procedure of choice to investigate mammographically detected nonpalpable breast lesions, having largely replaced needle-localized excisional biopsy. Although the sensitivity and specificity of this approach has been well documented,[2–10] increasing experience with core needle biopsy provides more information about the limitations as well as the benefits of the technique. Accurate diagnosis of breast lesions remains primarily the responsibility of the surgeon, and it is critical to understand in what circumstances core needle biopsy mandates further investigation.

Atypical ductal hyperplasia (ADH) of the breast is a premalignant lesion such that women with ADH excised in surgical biopsies have a moderately increased risk (four to five times that of age-matched control subjects) of having invasive carcinoma develop.[11–13] The difficulty of distinguishing ADH from ductal carcinoma *in situ* (DCIS) has been well established in the pathology literature. The criteria that Page and colleagues[13–15] have set forth for the diagnosis of DCIS requires involvement of at least two ducts; otherwise, a lesion that is qualitatively consistent with DCIS, but quantitatively insufficient, is identified as ADH. Furthermore, Lennington et al.[16] note that DCIS is often a heterogeneous lesion, with central areas of greatest atypia surrounded by areas of ADH. These observations lead us to postulate that the finding of ADH in a core needle breast biopsy may show DCIS at surgical excision.

METHODS

Breast core needle biopsy of 510 lesions was performed using either stereotactic guidance (414, 81%) (LORAD StereoGuide, Danbury, CT) or ultrasound guidance (96, 19%) (Acoustic Imaging, Tempe, AZ) between May 3, 1994, and June 12, 1996. Guidance method was determined by the method best imaging the lesion, radiologist preference, or randomization due to participation in a concurrent study. A 14-gauge needle was used with a 22-mm throw automated biopsy device (Manan Pro-Mag 2.2, or BIP, Turkenfeld, Germany). From 2 to 19 (mean, 7.5) core specimens were obtained per lesion. All abnormalities showing atypical ductal hyperplasia had at least five specimens obtained per lesion.

When using stereotactic guidance for mass lesions, an initial specimen was obtained from the center of the lesion, followed by samples obtained at 3 o'clock, 6 o'clock, 9 o'clock, and 12 o'clock. When using ultrasound guidance for mass lesions, a similar pattern was followed by sampling the center, anterior, posterior, cephalad, and caudad aspects of the lesion. All cases of microcalcifications were sampled using stereotactic guidance, in which individual calcifications were localized. For all lesions manifested primarily as microcalcifications, a specimen radiograph of the core samples was obtained. If the initial specimen did not contain microcalcifications, additional samples were obtained. Additional specimen radiographs were obtained in these cases to document satisfactory retrieval of microcalcifications.

Twenty-three core needle biopsy specimens (4.5%) showed atypical ductal hyperplasia on histologic examination, according to standard criteria.[13–15] The indication for biopsy in these cases was a nonpalpable mammographic abnormality. The number of core specimens obtained per lesion was 7.8 (range, 5–12). In these 23 cases, mammographic findings were as follows: 6 masses (26.1%), 15 microcalcification clusters (65.2%), 1 mass with microcalcifications (4.3%), and 1 lesion characterized only as architectural distortion (4.3%). Of the 15 lesions containing microcalcifications, the specimen radiograph showed microcalcifications in 12 (80%).

All 23 patients with the finding of ADH at core biopsy were advised to undergo surgical excision. However, one patient refused. That patient was taking tamoxifen for the treatment of a contralateral infiltrating ductal carcinoma with positive axillary lymph nodes diagnosed 1 year previously. One patient insisted on a simple mastectomy, with the specimen showing a focus of infiltrating carcinoma with associated lobular carcinoma *in situ* at the prior biopsy site. Results of the remaining 21 cases constitute the study population. The results of core needle and surgical specimens were reviewed and correlated.

RESULTS

Histopathologic analysis of the 510 core needle biopsies showed specific benign entities in 273 (52.6%), invasive malignant lesions in 112 (21.9%), DCIS in 22 (4.3%), ADH in 23 (4.5%), atypical lobular hyperplasia in 3 (<1%), lobular carcinoma *in situ* in 1 (<1%), and normal breast tissue or inadequate tissue for diagnosis in 76 (14.9%). Of this last group, many of the core biopsy specimens showing normal breast tissue were found to correspond to excisional biopsy specimens that had no pathologic diagnosis as well; however, further evaluation

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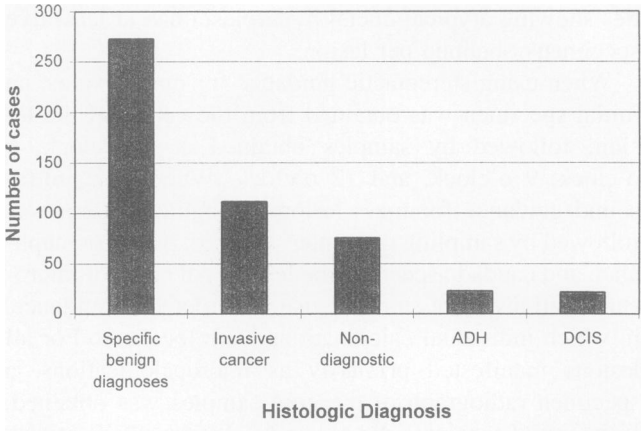

Figure 1. Histopathologic analysis of the 510 core needle biopsies.

of this subset awaits longer follow-up of these patients. These results are summarized in Figure 1.

For the 21 lesions diagnosed as ADH at core needle biopsy for whom subsequent surgical excision was performed, histopathologic study of the excisional biopsy specimen showed seven (33.3%) with carcinoma and five (23.8%) with atypical ductal hyperplasia. Eight (38.1%) surgical specimens contained benign histopathology without atypia and one (4.8%) contained lobular carcinoma *in situ* (Fig. 2). All seven of the carcinomas were identified as DCIS, of which two were high grade, four were intermediate grade, and one was low grade. In one specimen showing DCIS, an incidental tubular carcinoma was found near but distinct from the DCIS, and review of the mammogram substantiates that the microcalcifications that prompted biopsy were associated with DCIS.

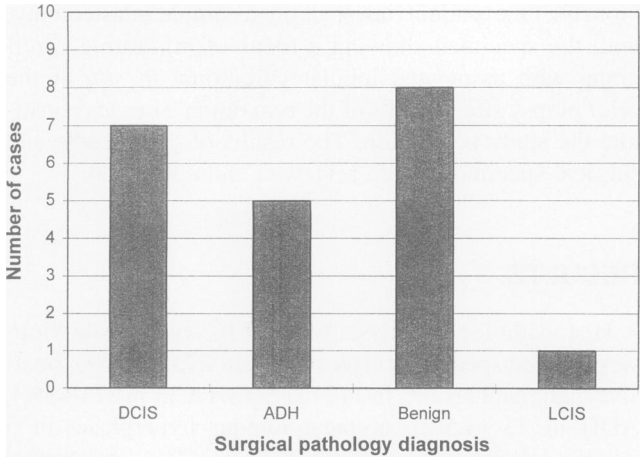

Figure 2. For the the 21 lesions diagnosed as atypical ductal hyperplasia at core needle biopsy for whom subsequent surgical excision was performed, histopathologic study of the excisional biopsy specimen showed seven with carcinoma and five with atypical ductal hyperplasia. Eight surgical specimens contained benign histopathology without atypia, and one contained lobular carcinoma *in situ*.

Table 1. CORRELATION OF MAMMOGRAPHIC APPEARANCE AND SURGICAL HISTOPATHOLOGY IN 21 CASES OF ADH AT CORE NEEDLE BIOPSY

	Surgical			
Mammographic	**Benign**	**ADH**	**Carcinoma**	**Total**
Calcifications	4	5	6	15
Mass	3	0	1	4
Mass with calcifications	1	0	0	1
Architectural distortion	1*	0	0	1
Total	9	5	7	21

* Case containing focal LCIS.
ADH = atypical ductal hyperplasia; LCIS = lobular carcinoma in situ.

The mammographic findings that initially prompted core biopsy were determined for the 21 patients in whom ADH was identified, and these were correlated to the histopathologic findings at surgical biopsy (Table 1). Although microcalcifications were the most common mammographic feature associated with DCIS in the surgical specimen (6/7, 86%), calcifications were the principal mammographic finding in 15 (71%) of 21 patients overall. Only 40% of these patients ADH associated with calcifications were found to have DCIS.

The histopathologic findings both in the core biopsy specimens and in the surgical specimens were reviewed prospectively in a multidisciplinary breast conference, permitting verification that the core biopsy site and the subsequent surgical excision were performed on the same lesion. This is shown in Figure 3, in which a photomicrograph of a core specimen diagnosed as atypical ductal hyperplasia is shown (Fig. 3A), and the corresponding surgical excision specimen (Fig. 3B) shows hemosiderin deposition from the prior core biopsy track adjacent to a region of florid DCIS.

DISCUSSION

In the past, optimal diagnosis of nonpalpable mammographic abnormalities has included needle-localized excisional biopsy, the "gold standard" for the pathologic confirmation of mammographically suspicious breast lesions. With the advent of core needle biopsy, new algorithms for diagnosis of nonpalpable lesions are required.

It has been accepted for some time that fine-needle aspiration biopsy of the breast does not faithfully distinguish ADH from DCIS,[17–19] and a finding of ADH at fine-needle aspiration biopsy commonly is an indication for surgical excision. Although core needle biopsy differs

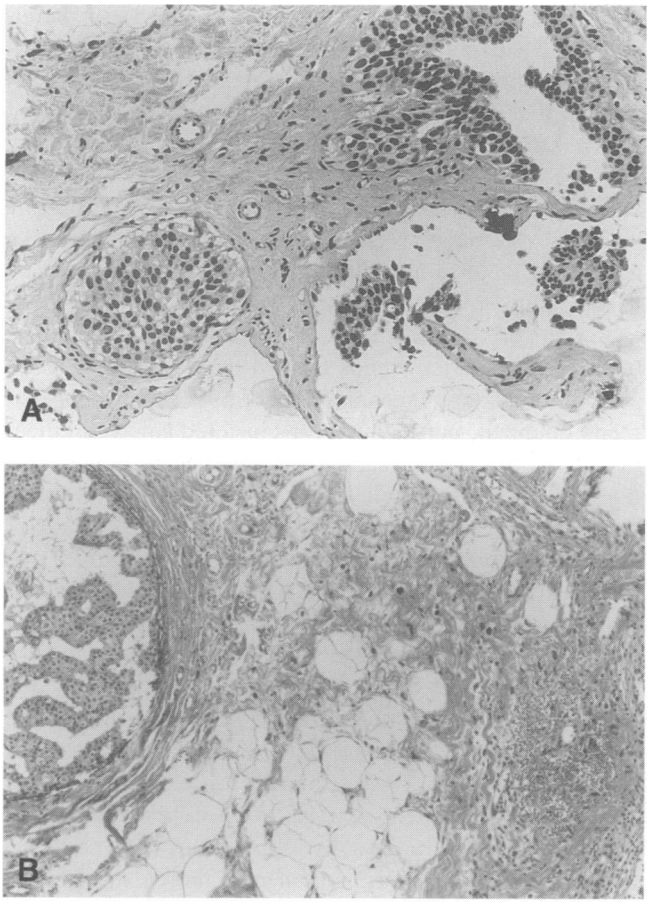

Figure 3. Photomicrograph of a core biopsy specimen diagnosed as atypical ductal hyperplasia is shown (Fig. 3A), and the corresponding surgical excision specimen (Fig. 3B) shows hemosiderin deposition from the prior core biopsy track adjacent to a region of florid ductal carcinoma *in situ*.

from fine-needle aspiration biopsy in that more tissue is obtained and architectural relations are preserved, our data show that core needle biopsy is unreliable in diagnosing ADH.

There are at least two potential explanations for the relation of ADH at core needle biopsy to DCIS. A first potential explanation is that ADH and DCIS are contiguous on a histologic spectrum, and the heterogeneity of breast lesions allows that ADH may be within or near an associated DCIS. This is illustrated by Lennington et al.,[16] who found ADH in 17% of surgically excised specimens of DCIS. A second potential explanation is that core biopsies, because of small sample size, may not satisfy quantitative criteria for the diagnosis of DCIS on the core biopsy specimen, even when DCIS is present in the breast. As developed by Page and colleagues,[20,22,24] the diagnosis of DCIS depends on three criteria: 1) cytologic features, 2) histologic pattern, and 3) anatomic extent of the lesion. With the limited tissue samples from core biopsy (each sample approximately 1 × 10 mm), it is not surprising to find instances where the volume of tissue sample is insufficient to permit a diagnosis of DCIS.

The pathology literature has highlighted the difficulty in diagnosing borderline epithelial lesions of the breast.[27] The philosophy of Azzopardi, as stated in his text *Breast Pathology*,[21] is that "names like 'atypical hyperplasia' should be avoided as far as possible" and that "the clinician should be told unequivocally that the lesion is benign or malignant." However, this philosophy has given way to a widely accepted concept that there is a continuum of epithelial breast lesions and that this needs to be understood by physicians involved in the care of patients with breast lesions.

A consensus meeting by the Cancer Committee of the College of American Pathologists[23] concluded that epithelial breast disorders should be categorized according to morphologic features and their associated risk of future development of invasive breast carcinoma. Initially, three categories were defined as follows: category 1, nonproliferative breast disease, no increased risk; category 2, moderate-to-florid hyperplasia, solid or papillary, 1.5- to 2-fold increased risk; category 3, atypical ductal or atypical lobular hyperplasia, 5-fold increased risk.[23] Page subsequently added category 4, ductal or lobular carcinoma *in situ*, 10-fold increased risk.[24] These categories, although undeniably helpful in systematizing the diagnosis of breast lesions, leave substantial room for interobserver variability, as has been shown nicely by Dr. Juan Rosai. In a survey published in *The American Journal of Surgical Pathology*, Dr. Rosai[23] asked five acknowledged leaders in surgical pathology to review ten slides of surgical excisions of proliferative ductal breast lesions. Of these ten cases, there were none in which all five pathologists agreed on the diagnosis. In three of the ten cases, diagnoses ranged from hyperplasia without atypia to frank carcinoma *in situ*. These results highlight the subjectivity and difficulty in diagnosing atypical ductal hyperplasia. Thus, the distinction between ADH and DCIS is difficult to make even when the entire lesion is evaluable histopathologically. It is not reasonable to expect, therefore, that even a skilled pathologist will be able to distinguish between ADH and DCIS reliably with a core biopsy sample. Until ultrastructural or immunohistochemical techniques are developed that may more accurately diagnose atypical ductal hyperplasia, the finding of ADH at core biopsy will necessitate a surgical excision to maximize the tissue available to the pathologist for the difficult diagnostic task.

Our data confirm that, in the context of clinical management, atypical ductal hyperplasia of the breast represents a high-risk lesion, which may well be associated with DCIS.[13] It would, therefore, be ideal if there were a way to identify lesions likely to be diagnosed as ADH by

Table 2. REVIEW OF THE LITERATURE REGARDING FINDINGS AT SURGICAL EXCISION OF LESIONS DIAGNOSED AS ADH AT CORE BIOPSY

Author	No. of Biopsies with ADH	No. of DCIS	No. of IDC	Total No. (%) of Cancers
Liberman[25]	21	8	3	11 (52)
Jackman[9]	16	6	3	9 (56)
Dahlstrom[10]	8	6*	1	7 (88)
Moore	21	7	0	7 (33)
Total	66	27	7	34 (52)

* These six lesions include both low grade DCIS and/or low grade infiltrating ductal carcinomas.
ADH = alcohol dehydrogenase; DCIS = ductal carcinoma *in situ*.

core biopsy based on their mammographic appearance to streamline patient management by proceeding directly to surgical excision. However, we confirm the work of Helvie,[28] who have reviewed the mammographic appearance and histologic correlation of atypical ductal hyperplasia of the breast and have found that, although clustered microcalcifications are the most common mammographic finding (found in 15, or 71%, of our cases, prompting core biopsy), there is no pathognomonic appearance of ADH.

Core needle biopsy is unreliable in diagnosing isolated atypical ductal hyperplasia. This finding is consistent with that of other published work. In three series recently published in the radiology and pathology literature, investigators have found significant rates of carcinoma, both *in situ* and invasive, associated with surgical excision after the finding of atypical ductal hyperplasia at core biopsy. Liberman et al.[25] reported that 11 (52%) of 21 patients with ADH at stereotactic core breast biopsy showed carcinoma at surgical excision. Of those with carcinomas, DCIS was found in eight, and invasive ductal carcinoma was found in three. In 16 patients with ADH diagnosed at stereotactic core biopsy, Jackman et al.[9] found nine (56%) having carcinoma at surgical excision (six DCIS, three invasive ductal carcinoma). Dahlstrom et al.[10] reported that seven of eight patients with ADH at core biopsy had carcinoma in the surgical specimens. Six were low grade *in situ* or ductal carcinomas or both and one was a focus of high-grade invasive ductal carcinoma. Taking the findings of these prior studies and the current report together, one can calculate an overall finding of carcinoma in 52% of lesions where ADH was found at core biopsy. This includes 27 (41%) of 66 *in situ* carcinomas and 7 (11%) of 66 invasive ductal carcinomas (Table 2).

Our study found a lower percentage of ADH (4.5%) than others have reported. However, the yield of malignant lesions overall in this series is consistent with experiences at other major institutions (26%). Thus, we do not believe that the lower percentage of patients diagnosed with ADH in our series reflects an inappropriately high biopsy rate. It may reflect differences between study populations; the average patient in the University of Virginia series of core biopsies is relatively young (52 years). An additional factor contributing to our findings may relate to the number of core biopsy specimens obtained per lesion. In prior evaluations of percutaneous core breast biopsy, we reported trends toward increasing diagnostic accuracy with an increasing number of core biopsy specimens obtained, particularly for clustered microcalcifications.[26] In the current series, we obtained no fewer than five specimens for each lesion showing atypical ductal hyperplasia.

Increased experience with core biopsy techniques and familiarity with the expected accuracy of percutaneous image-guided core biopsy for differing mammographic lesions can improve patient management. Careful, systematic approaches for identifying core biopsy results that are discordant with mammographic results should prompt excisional biopsy in appropriate situations. At least one such scenario is the finding of ADH at core biopsy. Our data show that, in many cases, core needle breast biopsy fails to distinguish accurately atypical ductal hyperplasia from DCIS. Furthermore, core needle biopsy may underestimate the presence of occult carcinoma in mammographically evident nonpalpable breast lesions. Thus, a diagnosis of atypical ductal hyperplasia at core biopsy of a nonpalpable breast lesion mandates a recommendation for surgical excision.

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Discussion

DR. EDWARD M. COPELAND, III (Gainesville, Florida): The surgical community is wrestling with the place that stereotactic core needle biopsy and core excisional biopsy of the breast have in the surgical armamentarium. One of the most attended exhibits at the American College of Surgeons this year was dedicated to the popularization of these two stereotactic techniques. Series published to date comparing core biopsy with surgical biopsy indicate a false-negative rate for the first 100 procedures of between 0% and 18%. The liability risks for these techniques have not yet been established. Dr. Hanks, Dr. Moore, and their colleagues have confirmed that atypical ductal hyperplasia warrants excisional biopsy because of the association with ductal carcinoma *in situ.*

What criteria do the authors use to determine core biopsy versus needle-guided excisional biopsy? Do you use stereotactic excisional biopsy and, if so, when?

How many excisional biopsies did your group do to confirm the accuracy of your stereotactic core technique before relying solely on the core for management? In other words, what was your false-negative rate in your first 100 cases of stereotactic core biopsy?

When excisional biopsy is required, do you then need to use needle localization technique to find the lesion, or do you just reenter the site of the stereotactic core biopsy tract?

My remaining query is about resident training. How have you insured that your surgical residents become competent in these stereotactic techniques? And do you expect them to be proficient and qualified to work independently with stereotactic modalities when finished with your residency training program?

DR. WILLIAM C. WOOD (Atlanta, Georgia): Dr. Hanks, Dr. Copeland, Dr. Moore. Thank you for the privilege of reviewing your manuscript and the very interesting observations that it bring to us. I have a comment as well, Dr. Copeland, and two questions.

The case for core needle biopsy is often made, as was implied with your slide initially, on an economic basis. You contrasted $550 as the charge for it compared to $1900 for an excision. I have some problems with that.

First, I think the case for core needle biopsy needs to be made from patient benefit and then ultimately the economic cost of that benefit examined. If you look not at charges but at costs, the difference narrows initially.

Then, if you look at the cost of the diagnosis rather than the first procedure, it's also different. Your costs were exclusive, as you mentioned, of pathology. If you add a $250 pathology charge, which is average in our community, and then you run through all the patients that you presented—the 53% who have a benign diagnosis and need no additional other biopsy versus all the others who need an additional procedure to follow-up on the initial biopsy, you would end up with a difference of only $350 per patient in charges—less in cost. That's still only the episode of the diagnosis.

If you look at the long-term cost, it may be somewhat different because unexcised mammographic abnormalities that have only been sampled will continue to be followed with increased mammographic views, and over the years, perhaps, with second biopsies if there is still concern about their appearance or their evolution. So, both the initial economic benefits and the initial patient benefits could conceivably reverse over time, somewhat