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ANATOMICAL PATHOLOGY

Long term clinical follow-up of atypical ductal hyperplasia and lobular carcinoma *in situ* in breast core needle biopsies

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Summary

Atypical ductal hyperplasia (ADH) and lobular carcinoma *in situ* (LCIS) may be associated with a relatively high incidence of invasive carcinoma and ductal carcinoma *in situ* (DCIS) on immediate excision when found on core needle biopsy of the breast. However, the long term significance of ADH and LCIS in a breast core needle biopsy is not as well characterised. We reviewed the results of all breast core needle biopsies with a diagnosis of ADH or LCIS and immediate excision from the years 2000–2004, and correlated the results with long term clinical follow-up. Of 175 biopsies with ADH, 53 (30.3%) had carcinoma (8 invasive, and 45 DCIS) at the time of immediate re-excision. Of 69 biopsies with LCIS, three (4.3%) had carcinoma (2 invasive, and 1 DCIS) at the time of immediate re-excision. A total of 14 (11.5%) patients with ADH and benign re-excisions developed invasive carcinoma (12) or DCIS (2) on follow-up. A total of 17 (25.8%) patients with LCIS and benign re-excisions developed invasive carcinoma (13) or DCIS (4) on follow-up. The risk of invasive carcinoma or DCIS on immediate re-excision was significantly higher for women with ADH than LCIS ($p < 0.001$). Women with LCIS developed significantly more invasive carcinomas and DCIS than women with ADH on long term follow-up ($p = 0.01$). Compared to women with fibrocystic changes (FCC) on core needle biopsy, the risk of developing invasive carcinoma or DCIS was significantly higher for women with ADH and benign initial re-excisions (95% CI 1.092–7.297, $p = 0.03$), and women with LCIS and benign re-excisions (95% CI 3.028–18.657, $p < 0.001$). Overall, 67/175 (38.3%) women with ADH and 20/69 (29.0%) women with LCIS on core needle biopsy either had carcinoma at the time of the biopsy or later developed carcinoma. Significantly more women with LCIS developed invasive carcinoma or DCIS than women with ADH on long term follow-up. The relative risk for ADH and LCIS on core biopsy with a negative excision compared with FCC was similar to that reported in the literature (ADH 1–7×, LCIS 3–19×).

Key words: Breast; neoplasia; carcinoma; atypical ductal hyperplasia; biopsy; core needle biopsy; mammotomy; LCIS; follow-up.

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INTRODUCTION

Atypical ductal hyperplasia (ADH) and lobular carcinoma *in situ* (LCIS) are known risk factors for the development of ductal carcinoma *in situ* (DCIS) and invasive carcinoma.[1] Numerous studies have shown that women with ADH have a breast cancer risk or odds ratio of about four times that of the general population,[2–7] and women with LCIS have a risk or odds ratio of about 3–8.[8–15]

However, most of these studies are based on women with excisional biopsies. The risks of invasive carcinoma or DCIS when ADH or LCIS is identified in a core needle biopsy may be different. Most studies have shown that ADH is associated with a relatively increased risk of invasive carcinoma or DCIS on immediate re-excision.[16–33] This presumably represents under-sampling of the carcinoma at the time of core needle biopsy, since carcinomas are rarely found when women with only ADH on excisional biopsy undergo immediate re-excision.[34] Whether LCIS is associated with an increased risk of invasive carcinoma or DCIS at immediate re-excision is controversial,[35–57] but the overall risk appears lower than that of ADH.[36,52,58] Data on the long term risk of invasive carcinoma or DCIS in women diagnosed with either ADH or LCIS on core needle biopsy are limited. In this study we present results of long term follow-up of a cohort of women all of whom presented with ADH or LCIS on core needle biopsy and underwent immediate re-excision.

METHODS

This study was approved by the institutional review board.

The results of breast core needle biopsy specimens interpreted from 1 January 2000 to 31 December 2004 at Baptist Hospital, Miami, FL, were reviewed. All biopsies with a diagnosis of ADH or LCIS were identified. Cases with both ADH and LCIS (22 cases) were initially separated but subsequently grouped in the LCIS category based on similar risk profiles [risk of invasive carcinoma/DCIS for LCIS alone 10/44 (25%), risk for ADH+LCIS 6/22 (27%)]. The majority (69%) of ADH cases were initially reviewed by at least two pathologists at the time of biopsy. These slides were re-reviewed and included in three prior studies.[17,36,58] Approximately two-thirds of the cases in the current series were included in those prior reports, but the previous reports included no long term follow-up, just the results of immediate excision. Only biopsies that fit the definition of ADH as outlined by others[59] were included in the analysis. In brief, these lesions were restricted to intraductal proliferations with some, but not sufficient, features of DCIS. Of the cases diagnosed as LCIS, 65.1% had E-cadherin testing which was negative. Cases of pleomorphic LCIS were excluded from this study. Management of LCIS on core needle biopsy was determined by the individual physician in consultation with the patient, and not all cases were excised. There were 64 women with a diagnosis of ADH and 27 women with a diagnosis of LCIS on core needle biopsy and a benign excision and no additional clinical follow-up that were excluded from further analysis. Overall there were 5218 core biopsies; 239 (4.6%) had ADH and 96 (1.8%) had LCIS.

All breast core needle biopsy specimens were obtained by the clinicians. Over 95% were performed by the radiology department, and consisted almost exclusively of 11 and 14 gauge core needle biopsy specimens performed under ultrasound or stereotactic guidance.

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All specimens were received fixed, and routinely processed. Up to five cores were processed in a single block; if more than five cores were present then an additional block was prepared. Each block was entirely sectioned to produce eight slides and between two and five levels per slide.

Clinical follow-up was obtained from the medical record. Information about chemoprevention in these women was not available. There was no significant difference in the way the patients were followed up in this study, though data on follow-up methods was limited to the available medical record.

Statistical analysis was performed using a two tailed Fisher's exact test. Disease free (invasive carcinoma and DCIS) survival analysis was performed using a Cox proportional hazard ratio (HR). A threshold of $p < 0.05$ was considered significant.

RESULTS

The results are summarised in Table 1.

Of 175 biopsies with ADH, 53 (30.3%) had carcinoma (8 invasive, and 45 DCIS) at the time of immediate re-excision. The remaining 122 cases had immediate re-excision without either invasive carcinoma or DCIS and additional clinical follow-up (mean follow-up 76 months, range 5–180).

Of 69 biopsies with LCIS, three (4.3%) had carcinoma (2 invasive, and 1 DCIS) at the time of immediate re-excision. The remaining 66 cases had immediate re-excision without either invasive carcinoma or DCIS and additional clinical follow up (mean follow-up 89 months, range 8–168). The risk of invasive carcinoma or DCIS on immediate re-excision was significantly higher for women with ADH than LCIS ($p < 0.001$).

A total of 14 (11.5%) patients with ADH developed invasive carcinoma (12) or DCIS (2) (all low to intermediate grade), 11 of which were in the same breast. Five (36%) carcinomas developed after at least 10 years of follow-up. Seven of the 12 invasive carcinomas were high grade (1/7 oestrogen receptor positive, 0/7 Her2Neu positive). The remaining five invasive tumours were low to intermediate grade (all oestrogen receptor positive and Her2Neu negative). A total of 17 (25.8%) patients with LCIS developed invasive carcinoma (13) or DCIS (4), 12 of which were in the same breast. Seven (41.2%) carcinomas developed after at least 10 years of follow-up. Eight of the invasive carcinomas were ductal and five lobular. All the invasive lobular carcinomas were oestrogen receptor positive and Her2Neu negative. Six of the invasive ductal carcinomas were low to intermediate grade (all oestrogen receptor positive, 1/8 Her2Neu positive). Two invasive ductal carcinomas were high grade (both oestrogen receptor negative, one Her2Neu positive). Women with LCIS developed significantly more invasive carcinomas and DCIS than women with ADH on follow-up ($p = 0.01$).

For comparison, of 100 patients with fibrocystic changes (FCC) on core needle biopsy, no re-excision, and additional clinical follow-up (mean 96 months, range 4–181), four women developed invasive carcinoma (all low-intermediate grade ductal type, oestrogen receptor positive, Her2Neu negative) and two developed DCIS (both high grade), all in the other breast.

Using a Cox proportional hazard ratio, invasive carcinoma and DCIS free survival was significantly lower for all women with ADH and benign initial re-excisions [95% confidence interval (CI) 1.092–7.297, $p = 0.03$], and women with LCIS and benign re-excisions (95% CI 3.028–18.657, $p < 0.001$) (Table 2). Kaplan–Meier curves are shown in Fig. 1. The 95% CI for relative risk (or fold risk) for ADH compared to FCC was 1–7 fold, while that of LCIS compared to FCC was 3–19 fold.

Overall, 67/175 (36%) women with ADH and 20/69 (29.0%) women with LCIS on core needle biopsy developed invasive carcinoma or DCIS.

Table 2 Cox proportional hazard ratio invasive carcinoma and DCIS free survival for ADH and LCIS versus FCC

	95% confidence intervals	*p* value
ADH	1.092–7.297	0.03
LCIS	3.028–18.657	<0.001

ADH, atypical ductal hyperplasia; FCC, fibrocystic changes; LCIS, lobular carcinoma *in situ*.

DISCUSSION

While there is a significant literature documenting the risk of progression to invasive carcinoma and DCIS in women with ADH and LCIS in excisional biopsies, and also a significant literature documenting the incidence of invasive carcinoma and DCIS on immediate excision in women with ADH or LCIS on core needle biopsy, the risk of progression over time for women with ADH or LCIS on core needle biopsy is not as well documented. There are at least two reasons why the risk for women with these lesion on core needle biopsy may be different than the risk associated with them on excisional biopsy. The first is sampling. Many authorities believe the

Table 1 Patient characteristics and follow-up

	FCC	ADH and IC or DCIS on immediate excision	ADH and benign immediate excision	LCIS and IC or DCIS on immediate excision	LCIS and benign immediate excision
Cases, *n*	100	53	122	3	66
Age, mean (range)	50.6 (25–81)	58.3 (37–79)	55.3 (25–82)	58.7 (49–73)	56.8 (39–77)
Follow up, months, mean (range)	96 (4–181)	NA	76 (5–180)	NA	89 (8–168)
IC on follow-up, *n* (%)	4 (4)	NA	12 (9.8)	NA	13 (19.7)
DCIS on follow-up, *n* (%)	2 (2)	NA	2 (1.6)	NA	4 (6.1)
IC or DCIS, *n* (%)	6 (6)	NA	14 (11.5)	NA	17 (25.8)
In same breast, *n* (%)	0 (0)	NA	11 (78.6)	NA	12 (70.1)

ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma *in situ*; FCC, fibrocystic changes; IC, invasive carcinoma; LCIS, lobular carcinoma *in situ*; NA, not applicable.