Published in final edited form as:

Ann Surg Oncol. 2017 January ; 24(1): 70–76. doi:10.1245/s10434-016-5512-9.

Long-Term Safety of Observation in Selected Women Following Core Biopsy Diagnosis of Atypical Ductal Hyperplasia

Rhiana S. Menen, MD¹, Nivetha Ganesan, BS¹, Therese Bevers, MD², Jun Ying, MS³, Robin Coyne, RN, MSN², Deanna Lane, MD⁴, Constance Albarracin, MD⁵, and Isabelle Bedrosian, MD¹

¹Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

²Department of Cancer Prevention, The University of Texas MD Anderson Cancer Center, Houston, TX

³Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

⁴Department of Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX

⁵Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX

Abstract

Purpose.—Atypical ductal hyperplasia (ADH) found on core biopsy is associated with an upgrade to carcinoma in 10–30 % of women, thus surgical excision remains the standard of care. This study compares the incidence of breast cancer in women with ADH who were observed with those who underwent surgical excision of the ADH site.

Methods.—Our departmental, prospectively maintained registry was reviewed to identify patients with ADH diagnosed by core biopsy. Surgically treated patients were excluded if upstaged to carcinoma following excision for ADH diagnosis. Breast cancer events were classified as index site (site of ADH biopsy), ipsilateral breast unrelated to index site, or contralateral breast.

Results.—Overall, 175 women met the study criteria; 125 were observed and 50 underwent excision. With a median follow-up of 3 years, 14 breast cancer events were noted in 13 patients. In the surgery group, six women developed breast cancer (12 %), including one bilateral, compared with seven cancers (5.6 %) in the observed group ($p = 0.14$). Index site events and ipsilateral cancers were the same in both groups [2 vs. 0.8 % ($p = 0.49$) and 4 versus 4.8 % ($p = 1.00$), respectively]. All contralateral cancers occurred in the surgical group (8 vs. 0 %; $p < 0.01$). A prior history of breast cancer was the only variable associated with subsequent breast cancer events (hazard ratio 12.53, 95 % confidence interval 3.30–47.57).

Conclusion.—Observation is appropriate in selected women with ADH on core biopsy. Index site failures are rare and are superseded by cancer risk elsewhere in the breast.

Atypical ductal hyperplasia (ADH) is recognized as not only a risk marker for the development of breast cancer but also as a precursor lesion that shares molecular similarities

to ductal carcinoma in situ (DCIS) and invasive breast cancer.¹ The fact that ADH can progress to carcinoma, coupled with reports that ADH found on core needle biopsy (CNB) of a mammographic abnormality can be associated with an upgrade rate to non-invasive and invasive breast cancer in 18–31 % of cases,^{2,3} has resulted in the practice of routine excision of all ADH lesions. However, in many instances, no upgrade lesion is identified, and therefore strategies that may reliably identify ADH patients at low risk of upgrade are of great interest to allow for selection of women who can be safely observed. A number of approaches have been described in order to rule out associated cancer, including different methods of CNB, stratification of the extent of calcifications, and proportion of calcifications removed.^{4,5}

We have previously published criteria by which ADH lesions found on core biopsy can be triaged according to the risk of upgrade to an associated carcinoma.⁵ In a series of 140 cases of patients presenting with calcifications but no mass lesions on mammography, we reported that removing <95 % of calcifications significantly correlated with the rate of upgrade to carcinoma. With regard to histology, significant predictors of upgrade included the number of involved terminal duct-lobular units (TDLU>2), presence of significant cytologic atypia, and presence of necrosis. Using these combined criteria led to an upgrade rate of 3 % for the subset of women with low risk features. We therefore concluded that select cases of ADH may be safe to observe in patients with well-sampled lesions without necrosis and a limited number of affected TDLUs.

Similar criteria were recently reported from the group at the Mayo Clinic, who evaluated a model to predict upgrade in patients diagnosed with ADH on CNB. The overall upgrade rate was 16.1 %, and they similarly concluded that features on core biopsy most strongly associated with upgrade were imaging estimated percentage of the lesion removed, individual cell necrosis, and number of ADH foci. Using this criteria, upgrade rates as low as 5.0 % could be achieved in women with no necrosis and either 1 focus with 50 % removal or >1 focus with 90 % removal of the sample.⁶ Although these series can provide encouraging data to support selected observation, no reports exist regarding the long-term safety of this approach. The objective of this study was therefore to review the incidence of breast cancer within the group of women with a CNB diagnosis of ADH and for whom observation was recommended following multidisciplinary review.

MATERIALS AND METHODS

Cohort Selection

The Department of Cancer Prevention at the University of Texas MD Anderson Cancer Center prospectively maintains a database of patients with high-risk pathology presented and discussed at our interdepartmental multidisciplinary conference. This database was interrogated to identify 233 patients diagnosed with ADH between January 2004 and August 2011. No known BRCA mutation carriers were included. All patients were reviewed by a multidisciplinary team including radiologists, pathologists, internists with a practice focus in high-risk populations and cancer prevention, and surgeons; treatment recommendations were captured within the database. As per our previous publication, patients with <3 TDLUs involved, >90 % removal of calcifications, and no necrosis were eligible for observation after

discussion within the multidisciplinary group.⁵ Over the study years, this criteria was expanded and, in some cases, patients with no mass lesion or architectural distortion, and >50 % of calcifications removed with radiologist and pathologist agreement that the lesion was well-sampled, became eligible for observation. Patients who did not meet these criteria were excised. Individual patient records were reviewed to capture additional demographics and long-term patient outcomes. Cancer events included both non-invasive DCIS and invasive cancers. Cancer events were classified as cancer at the index site (site of ADH biopsy), ipsilateral breast unrelated to the index site, or contralateral breast. Mammographic images were reviewed by a breast radiologist (DL), and recurrence in the ipsilateral side was classified as an index recurrence if the cancer was within 3 cm of the site of the ADH biopsy. Patients were excluded from the analysis if they lacked follow-up ($n = 34$), or had ADH based on excisional biopsy ($n = 10$). Of the 189 patients who remained, 64 underwent surgery for a diagnosis of ADH, of which 14 were excluded for upgrade on biopsy. The remaining 50 patients who underwent surgical excision for ADH with benign findings, in addition to the 125 patients who were clinically observed, form the 175 patients in this study (Fig. 1). Routine follow-up of this population included annual clinical examination and mammogram. Magnetic resonance imaging (MRI) was not routinely used for screening. This study was approved by the Institutional Review Board (IRB).

Follow-Up

Follow-up was defined as the number of days between the date of the multidisciplinary conference during which patient management was discussed and the date of last imaging follow-up. In women who developed a subsequent cancer, follow-up was defined as the number of days between the date of the multidisciplinary conference date and the date of cancer diagnosis. Median follow-up was 1085 days in the observation group and 1134 days in the surgical group ($p = 0.94$).

Statistical Analysis

Chi square or Fisher's exact test analysis was performed as univariate analysis to evaluate the association between categorical variables and subsequent breast cancer events or surgery. Student's t test was performed as univariate analysis for continuous variables. Multivariable cox regression analysis was performed to identify variables that were significantly associated with subsequent breast cancer events over the length of follow-up.

RESULTS

Clinical and Demographic Characteristics

Patient characteristics for the cohort, including the subset who were lost to follow-up, are included in Table 1. The majority of women were over 50 years of age, White, and had no prior breast cancer history. In the observed group ($n = 125$), 69 women (55 %) were recommended to resume annual surveillance following the ADH core biopsy diagnosis, 52 women (42 %) were recommended for interval 6 month imaging, and 4 women (3 %) required additional workup and biopsy. Forty-two women (24 %) in this study received chemoprevention. The group treated surgically and those observed were well-balanced with regard to age, race, prior breast cancer history, receipt of chemoprevention, and median

follow-up (Table 1). With regard to the subset of patients who were lost to follow-up ($n = 34$), no differences in age, race, and prior breast cancer history were noted compared with observed or surgically treated patients (Table 1).

Breast Cancer Events

Cancer events are detailed in Fig. 1. Overall, a total of 13 patients experienced 14 breast cancer events during the follow-up period. DCIS accounted for eight events, while six events were reported as invasive. In the surgery group, six women had seven breast cancer events (6/50, 12 %), one of which was bilateral. Of these, three (3/50, 6 %) were in the ipsilateral breast, with only one (1/50, 2 %) occurring at the index site. In the contralateral breast, four breast cancer events were reported (4/50, 8 %). In the observed group, there were seven cancer events (7/125, 5.6 %), all of which were in the ipsilateral breast, and the majority occurred remote from the index site, with only one occurring at the index site (1/125, 0.8 %). Of note, index site events were similar in both groups (2 vs. 0.8 %; $p = 0.49$), as were ipsilateral cancers outside of the index site (4 vs. 4.8 %; $p = 1.00$). Conversely, all contralateral cancers occurred in the surgery group (0 vs. 8 %; $p < 0.01$). When including both observed and excised groups, ipsilateral cancers accounted for 10/14 (71.4 %) of all subsequent breast cancer events in this cohort. The Kaplan–Meier analysis for overall breast cancer events is depicted in Fig. 2. The overall probability of any breast cancer event at 5 years of follow-up was approximately 17 %.

Factors Associated with Subsequent Breast Cancer

Univariate analysis of the clinical and demographic variables demonstrated that only prior breast cancer history was significantly associated with subsequent breast cancer risk in this population of women with ADH ($p = 0.02$) (Table 2). Age, race, use of chemoprevention, and surgical excision did not significantly impact the risk of subsequent breast cancer events. When follow-up time was taken into account, multivariate Cox proportional hazards regression analysis showed that the association with a prior history of breast cancer remained significant even after adjusting for all other variables [hazard ratio 12.53, 95 % confidence interval (CI) 3.30–47.57] (Table 3).

DISCUSSION

Findings of ADH on biopsy have been associated with an upgrade to DCIS or invasive cancer in 18–31 % of cases;^{2,3} therefore, our findings of a 21 % rate of upgrade are consistent with these reports. We have previously published that selected groups of patients have a low risk of upgrade and these women may be considered for observation.⁵ Our aim in this study was to evaluate the robustness of this algorithm by examining long-term outcomes in the observed women. Our data show that, in selected cases, observation following core biopsy diagnosis of ADH is safe and does not result in higher rates of cancer at the index site. To our knowledge, these data represent the first study reporting long-term cancer events following observation in women diagnosed with ADH on core biopsy.

Although we found no difference between the observed and excised groups with regard to the total number of breast cancer events, overall, three quarters of the cancer events in either

group occurred in the ipsilateral breast. This finding of higher ipsilateral subsequent cancers has been reported elsewhere. Collins et al. noted that approximately 60 % of breast cancers occur in the ipsilateral breast of women with biopsy-proven atypical hyperplasia.⁷ In the Mayo series of long-term outcomes in ADH patients reported by Degnim et al., subsequent cancers were also more frequent in the ipsilateral breast, although this difference did not reach statistical significance.⁸ Such data reinforce the well-established concept that ADH is a marker of increased risk for breast carcinoma, and underscores the need for close monitoring and chemoprevention, rather than surgical excision of the index site.

The predicted 5 year probability of any breast cancer event was approximately 17 %, which, in our modeling, stayed steady over a 10 year follow-up. This is higher in the short-term than other published reports, although consistent with other long-term data.^{8,9} For example, using the Mayo Benign Breast disease cohort of 388 women, Degnim et al. stratified patients with atypia into risk groups, and reported that the development of DCIS and invasive ductal cancers was 19.9 % over 13.7 years.⁸ In another series, the estimated 10 year cancer risks for developing breast cancer were 17.3 % for ADH and 26.0 % for patients with severe ADH.⁹ The significantly higher rate of subsequent cancer we observed in the first 5 years after ADH diagnosis in our cohort may be due to a number of factors. Our cohort had a relatively high rate of women with a prior personal history of breast cancer, and approximately 13 % of women in our series had a prior breast cancer event compared with 7.8 % of women in the Mayo series. Indeed, of all variables studied, a prior history of breast cancer was the only factor significantly associated with any subsequent breast cancer event. It is also possible that a small number of total breast cancer events in this cohort may have led to an overestimation of the 5 year probability of developing subsequent cancer.

Surprisingly, we did not see an association between age and subsequent breast cancer risk, nor uptake of chemoprevention and subsequent breast cancer risk, both factors well-established to impact the risk of cancer events after ADH diagnosis.^{8–13} For instance, Degnim et al. showed that the relative risk (RR) of cancer for women <45 years of age with ADH was 6.76 (95 % CI 3.24–12.4).⁸ In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study it was noted that tamoxifen use reduced the risk of invasive cancer in patients with ADH by 86 %, which was a much greater benefit than the 50 % risk reduction seen in the cohort overall.^{10,11} Other series similarly confirm the significant efficacy in risk reduction achieved by women with ADH who receive chemoprevention.^{9,12,13} This discrepancy between our findings and others in the literature likely reflects sample size considerations. Our study did not include many young patients, with only 27 % of all patients aged <50 years. Furthermore, uptake of chemoprevention was low in our study, with only one-quarter of patients opting to take such intervention. This rate, although comparable with rates of use in other series, likely impacted our ability to be powered to show association between chemoprevention and subsequent cancer events.

There are other variables that are known to impact the risk of breast cancer that we did not include in our analysis for a number of reasons, including family history, which has long been established as a breast cancer risk factor; however, recent reports by Degnim et al. and Collins et al. suggest that the effect of family history is mitigated in women with atypia.^{8,14}

Similarly, we did not have an opportunity to include histologic features of risk such as involution as this information is not part of standard pathologic reporting.

There are a number of limitations to our observations. The results are drawn from an institutional registry with a relatively small sample size and, while prospective in nature, cannot fully address biases that could impact the long-term outcomes we observed. In addition, the pathologic findings of ADH were based on review by any member of our breast pathology group and not subject to a central review to reach consensus, if required. Given the known challenges and inter-pathologist variability in interpretation of ADH,¹⁵ this may have introduced both over- and underestimates in the diagnosis of ADH. Lastly, our practice has evolved over the last decade since we first started to implement a standardized approach to this patient population. Most notably, we have lowered the threshold for mammographic sampling and, in many cases, will now accept $\geq 50\%$ removal of calcifications, coupled with low-risk histologic findings, as appropriate for observation, which creates some heterogeneity in the study population. Important strengths to our study include the multidisciplinary review of each case in order to establish consensus management at the time of ADH diagnosis, as well as the re-review by a single breast radiologist (DL) of all the cancer events to classify their relationship to the index ADH biopsy site.

CONCLUSIONS

Careful multidisciplinary review of ADH cases, coupled with a prediction algorithm for upgrade risk, can identify a subset of women who may safely be observed. These findings warrant more rigorous, prospective, multi-institutional validation.

Acknowledgments

FUNDING This work was supported by a University of Texas MD Anderson Cancer Center support Grant (5 P30 CA016672 36).

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FIG. 1.
Outcomes of women with ADH on core biopsy treated with surgery versus observation.
ADH atypical ductal hyperplasia, *CNB Dx* core needle biopsy diagnosis

FIG. 2.
Kaplan–Meier analysis for overall breast cancer events

Table 1

Characteristics of patients in the observation and surgical groups

	Observation (<i>n</i> = 125)	Surgery (<i>n</i> = 50)	<i>p</i> Value	Lost to follow-up (<i>n</i> = 34)	<i>p</i> Value ^a
Age, years					
<50	34 (27.2)	14 (28)	0.91	7 (20.5)	0.40
>50	91 (72.8)	36 (72)		27 (79.4)	
Race					
Asian	3 (2.4)	3 (6)	0.09	2 (5.8)	0.89
Black	10 (8)	9 (18)		3 (8.8)	
Hispanic	10 (8)	5 (10)		2 (2.5)	
White	102 (81.6)	33 (66)		27 (79.4)	
Prior breast cancer history					
No	108 (86.4)	44 (88)	0.78	29 (85.3)	0.79
Yes	17 (13.63)	6 (12)		5 (14.7)	
Chemoprevention					
Yes	29 (23.2)	13 (26)	0.70	NA	NA
No	96 (76.8)	37 (74)		NA	
Disposition after core biopsy					
Annual follow-up	69 (55.2)	0	NA	11 (32.3)	<0.01
Imaging within 6 months	52 (41.6)	0		2 (5.9)	
Further biopsy	4 (3.2)	0		0	
Surgery	0	50 (100)		21 (61.7)	
Median follow-up, days	1085	1134	0.94	NA	NA

Data are expressed as *n* (%)NA in data column not available; NA in *p* value columns not applicable^a *p* Value: comparison of patients with follow-up (observation and surgery groups) and those lost to follow-up

Table 2

Univariate analysis of clinical and demographic variables by subsequent breast cancer events

	No subsequent cancer	Subsequent cancer	<i>p</i> Value
Age, years			
<50	42 (87.5)	6 (12.5)	0.12
>50	120 (94.5)	7 (5.5)	
Race			
Asian	5 (83.3)	1 (16.7)	0.51
Black	17 (89.5)	2 (10.5)	
Hispanic	14 (93.3)	1 (6.7)	
White	126 (93.3)	9 (6.7)	
Prior breast cancer history			
No	144 (94.7)	8 (5.3)	0.02
Yes	18 (78.3)	5 (21.7)	
Chemoprevention			
Yes	39 (92.9)	3 (7.1)	1.00
No	123 (92.5)	10 (7.5)	
Surgery			
No	118 (94.4)	7 (5.6)	0.14
Yes	44 (88)	6 (12)	

Data are expressed as *n* (%)

Table 3

Multivariate analysis of variables associated with subsequent breast cancer

Parameter	HR	95 % CLs
Age>50 years	0.32	0.10–1.02
Race		
Asian	1.95	0.22–17.12
Black	1.01	0.21–4.84
Hispanic	0.65	0.08–5.42
Prior cancer history	12.53	3.30–47.57
Chemoprevention	0.80	0.20–3.16
Surgery	2.52	0.80–7.96

HR hazard ratio, *CLs* confidence limits