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Research Article

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Understanding the Premalignant Potential of Atypical Hyperplasia through Its Natural History: A Longitudinal Cohort Study

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Abstract

Atypical hyperplasia is a high-risk premalignant lesion of the breast, but its biology is poorly understood. Many believe that atypical ductal hyperplasia (ADH) is a direct precursor for low-grade ductal breast cancer, whereas atypical lobular hyperplasia (ALH) serves as a risk indicator. These assumptions underlie current clinical recommendations. We tested these assumptions by studying the characteristics of the breast cancers that develop in women with ADH or ALH. Using the Mayo Benign Breast Disease Cohort, we identified all women with ADH or ALH from 1967 to 2001 and followed them for later breast cancers, characterizing side of breast cancer versus side of atypia; time to breast cancer; type, histology, and grade of breast cancer, looking for patterns consistent with precursors versus risk indicators. A total of 698 women with atypical hyperplasia were followed a mean of 12.5 years; 143 developed breast cancer. For both ADH and ALH, there is a 2:1 ratio of ipsilateral to contralateral breast cancer. The ipsilateral predominance is marked in the first 5 years, consistent with a precursor phenotype for both ADH and ALH. For both, there is a predominance of invasive ductal cancers with 69% of moderate or high grade. Twenty-five percent are node positive. Both ADH and ALH portend risk for ductal carcinoma *in situ* and invasive breast cancers, predominantly ductal, with two thirds moderate or high grade. The ipsilateral breast is at especially high risk for breast cancer in the first 5 years after atypia, with risk remaining elevated in both breasts long term. ADH and ALH behave similarly in terms of later breast cancer endpoints. *Cancer Prev Res; 7(2); 1–7. ©2014 AACR.*

Introduction

Breast biopsies are performed commonly, for either palpable or more commonly, mammographic concerns. In this latter group, atypical ductal or lobular hyperplasia is diagnosed in 8% to 10% of samples (1). Atypia represents a high-risk premalignant lesion of the breast, conveying a relative risk of approximately 4 for a later breast cancer (1–4) with a cumulative incidence of 29% at 25 years (5, 6). In proposed models of breast carcinogenesis, atypia occupies a bridging position between benign and malignant disease (4, 7, 8). Despite the frequency and high-risk nature of atypia, its biology is still poorly understood. In particular, it is unclear if these lesions represent true precursors or rather, histologic manifestations of a tissue bed at increased risk. Atypical ductal hyperplasia (ADH) is generally considered a direct precursor of low-grade ductal carcinoma *in situ* (DCIS) and thus, low-grade invasive ductal cancer, whereas the precursor(s) of higher-grade DCIS and invasive ductal cancer remain unknown (9–11). Atypical lobular hyperplasia (ALH) is thought to occupy a position in the evolution of lobular carcinoma but is also considered a risk indicator for a later breast cancer in either breast (8, 12, 13). Notably, current clinical recommendations are that ADH lesions should be completely excised whereas ALH lesions found on a core may, as risk indicators, not require excision (14, 15).

Better understanding of the natural history of atypical hyperplasia, ductal, and lobular, will advance both our understanding of breast carcinogenesis and our clinical management of these high-risk patients. If an atypia serves as a direct precursor, one would expect a preponderance of subsequent breast cancers to occur in the same breast, with shared histologic features, perhaps with a shorter time to occurrence. Subsequent carcinoma *in situ* is likely to be more common. By contrast, if an atypia is a risk indicator, later breast cancers should occur with equal frequency in both breasts, with variable histology and time to occurrence.

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We previously published the risk factors of a series of 331 women with atypical hyperplasia diagnosed at the Mayo Clinic from 1967 to 1991 (5). Here we have extended our series through 2001 and now report on 698 women with atypia who have been followed an average of 12.5 years for later breast cancers. We present the features of the breast cancers—side of breast cancer versus side of atypia, time to cancer, histologic type of breast cancer versus type of atypia, and grade—so as to further understanding of the nature of both ductal and lobular atypical hyperplasia.

Materials and Methods

Our initial Benign Breast Disease Cohort included all women who had a benign breast biopsy at Mayo Clinic (Rochester, MN), from January 1, 1967 to December 31, 1991 (3). We have subsequently extended the cohort through December 31, 2001, which now includes 13,652 women. For the current report, we identified those women who had histologic findings of atypical hyperplasia on breast biopsy between January 1, 1967 and December 31, 2001. Follow up for breast cancer events (including both invasive cancer and DCIS) and risk factor information were obtained for all women with ADH or ALH, using the Mayo medical record, Mayo Tumor Registry, and a study-specific questionnaire to capture diagnoses made outside the Mayo Clinic system. For the breast cancers, medical records and tissue slides were obtained for review. Our study pathologist verified the histology on cancers diagnosed at other institutions. A diagnosis of ADH or ALH was based on the criteria of Page and colleagues (16, 17) as we have previously reported (5). For each example of atypical hyperplasia, the number of separate foci was determined. Multifocal atypia, as seen on a single slide, required its presence in more than one terminal duct lobular unit as defined by clear separation from another by nonspecialized interlobular stroma (5). The definitions of laterality were: ipsilateral, cancer occurring in the same breast as the atypia biopsy; contralateral, cancer in the opposite breast; and bilateral, the occurrence of cancer in both breasts within 6 months of each other. Invasive breast carcinomas were graded according to the Nottingham criteria of Elston and Ellis (18). Cases of DCIS were classified by nuclear grade as follows: grade 1—tumor cells had small, monotonous nuclei with inconspicuous nucleoli and rare mitoses, usually forming cribriform and/or micropapillary structures; grade 2—tumor cells showed significant nuclear enlargement, with modest pleomorphism and presence of nucleoli with readily identified mitotic activity; and grade 3—the involved ducts generally showed prominent comedo type necrosis and tumor cells showed marked nuclear enlargement, often with macronucleoli, and abundant mitotic activity.

Follow up was defined as the number of days from atypia biopsy to date of breast cancer diagnosis, death, or last contact. We estimated relative risks with standardized incidence ratios (SIR) and 95% confidence intervals (CI), dividing observed numbers of incident breast cancers by expected counts. We used the Iowa Surveillance Epidemiology and End Results (SEER) registry as the reference population because of its proximity to the Mayo Clinic catchment area and similar population demographics compared with our cohort (3). We formally assessed heterogeneity in the relative risks across different demographic and histologic attributes using Poisson regression analyses, as described previously (3). We displayed observed and expected event rates using cumulative incidence curves, accounting for the effects of death as a competing risk (19). We compared cancer-related features across type of atypia (ALH vs. ADH), subset to breast cancer events, using χ^2 tests for categorical variables and t tests for continuous variables.

The study protocol, including patient contact and follow-up methods, was approved by the Mayo Clinic Institutional Review Board with methods previously described (3, 5).

Results

This cohort of 698 women with atypical hyperplasia had biopsies performed 1967 to 2001 at the Mayo Clinic. Their risk factors for later breast cancer are displayed in Table 1. In this cohort, there are 330 women with ADH, 327 with ALH, and 32 with both ADH and ALH. Of the 698 women, 101 had a core biopsy for diagnosis whereas the remainder had an excisional biopsy. As we have shown before, and now confirm in a larger cohort, risk of breast cancer is increased in younger women with atypia, those with multiple foci of atypia, and those with less age-related lobular involution (5, 20). As before, a woman with atypia who also has a family history of breast cancer does not experience further elevation of risk, beyond that of the atypia itself.

Over a mean of 12.5 years of follow up (median 12.1 years), 143 (20.4%) of these 698 women developed breast cancer. The cumulative incidence of breast cancer is shown in Fig. 1, revealing a steady increase over time with 29% of these women developing breast cancer at 25 years after atypia biopsy. Characteristics of the 143 women who developed breast cancer are provided in Table 2 and Fig. 2. Regarding side of later breast cancer, the ratio of ipsilateral to contralateral events is approximately 2:1—for both ADH and ALH. Time to breast cancer is displayed in Fig. 2A and Table 2. Comparing the time distributions by 5-year increments for ADH versus ALH, there is no significant difference (Table 2; $P = 0.22$). For all atypias, breast cancers developing within 5 years of the biopsy were more likely to occur in the ipsilateral breast than those developing more than 5 years removed from the atypia (80% vs. 62%, χ^2 $P = 0{\cdot}04$). This difference was more pronounced in women with ADH (82% ipsilateral in first 5 years vs. 58% ipsilateral after 5 years, $P = 0.06$) than in those with ALH (74% ipsilateral in first 5 years vs. 64% thereafter, $P = 0.45$; Fig. 2A).

For all the women with atypia, 19% of the breast cancers are ductal carcinoma *in situ* (DCIS), with 81% invasive breast cancers (Fig. 2B and Table 2). Specifically in women with ADH, about 25% of later breast cancers are DCIS, in both the ipsi- and contralateral breast. With ALH, 13% of

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Table 1. Risk factors for breast cancer among the 698 women with atypia from the Mayo Benign Breast Disease Cohort

Variable	Group	Number	Expected	Observed	SIR (95% CI)	*P* value
Overall atypia cohort	All atypias	698 (100%)	33	143	4.34 (3.66, 5.12)	
Age at atypia	<45	100 (14.3%)	3	17	5.45 (3.17, 8.73)	0.04
	45-55	233 (33.4%)	11	59	5.43 (4.13, 7.01)	
	>55	365 (52.3%)	19	67	3.54 (2.74, 4.49)	
Type of atypia	ADH	330 (47.9%)	15	60	3.93 (3.00, 5.06)	0.54
	ALH	327 (47.5%)	16	75	4.76 (3.74, 5.97)	
	ADH and ALH	32 (4.6%)	2	7	4.36 (1.75, 8.96)	
Number of atypical foci	1	410 (59.9%)	20	65	3.19 (2.46, 4.07)	<0.001
	2	161 (23.5%)	7	40	5.53 (3.95, 7.53)	
	3+	113 (16.5%)	5	37	7.61 (5.36, 10.49)	
Extent of lobular involution	None	75 (11.4%)	3	21	7.66 (4.74, 11.72)	<0.001
	Partial	428 (65.2%)	21	98	4.63 (3.76, 5.65)	
	Complete	153 (23.3%)	7	14	1.91 (1.04, 3.20)	
Family history of breast cancer	None	372 (59.1%)	18	70	3.91 (3.05, 4.94)	0.23
	Weak	151 (24%)	7	39	5.54 (3.94, 7.57)	
	Strong	106 (16.9%)	6	24	4.19 (2.68, 6.23)	
Calcifications	NO	173 (24.8%)	9	40	4.63 (3.31, 6.31)	0.64
	YES	525 (75.2%)	24	103	4·24 (3·46, 5·14)	

SIR, standardized incidence ratio comparing observed number of breast cancer events to those expected based on Iowa SEER data; *P*-value, test for heterogeneity of SIR across levels of given characteristic. Family history criteria: strong = 1 first-degree relative (FDR) with breast cancer before age 50, or 2 or more relatives with breast cancer, with at least one a FDR; weak = any lesser degree of family history.

the later breast cancers are DCIS versus 87% invasive ($P = 0.07$ for ADH vs. ALH). Regarding histology of later breast cancers (Fig. 2C and Table 2), for women with ADH, 78% of later breast cancers are ductal, and 22% lobular or other histologies. For ALH, 77% of breast cancers are ductal, with 23% lobular or other histologies ($P = 0.14$). These proportions are seen in both the ipsi- and contralateral breasts. The grade of subsequent breast cancers is shown in Fig 2D and Table 2. There are 42 women with initial ADH, for whom grade of later breast cancer is known: 31% developed a grade 1 breast cancer, 43% a grade 2, and 26% a grade 3 breast cancer. The figures for the 49 women with ALH and known grade of breast cancer are: 31% grade 1, 53% grade 2, and 16% grade 3 ($P = 0.46$ for ADH vs. ALH).

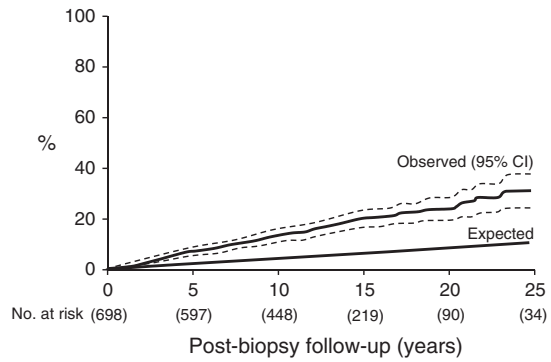

Figure 1. Cumulative risk of breast cancer over time. Expected breast cancer events were calculated by applying age- and calendar period-stratified person-years of observation to Iowa SEER incidence rates. Observed and expected events cumulated after accounting for death as a competing risk.

For the invasive breast cancers, nodal status is known for 95: 75% are node negative, and 25% are node positive. For the invasive breast cancers, mean tumor size is 1.8 cm (SD = 1.6 cm). No differences in these characteristics were observed in the women with ADH versus ALH. The mean time from atypia diagnosis to breast cancer is 10.3 years (SD = 7.7 years).

Discussion

To our knowledge, this is the largest cohort of women with atypical hyperplasia followed long term for later breast cancer events, where central pathology is available for all the original atypia samples and the majority of the subsequent breast cancers. There are sufficient numbers of both ADH and ALH to allow comparisons of their natural histories. In this longitudinal cohort study, we show that ADH and ALH are associated with similar long-term breast cancer outcomes. Women with either ADH or ALH developed breast cancers with a fairly typical distribution of histologies, with ductal cancers predominating. About two thirds of the breast cancers (69%) are moderate or high grade. The cancer risk in the ipsilateral breast is twice that of the contralateral

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Table 2. Characteristics of breast cancers by type of atypia[a]

	ADH ($N = 60$)	ALH ($N = 75$)[a]	P value[b]
Breast cancer sidedness			0.79
Missing	2	4	
Bilateral	3 (5.2%)	2 (2.8%)	
Ipsilateral	37 (63.8%)	46 (64.8%)	
Contralateral	18 (31.0%)	23 (32.4%)	
Cancer type			0.07
Missing	1	6	
Invasive	44 (74.6%)	60 (87.0%)	
In situ	15 (25.4%)	9 (13.0%)	
Invasive histology grouping			0.14
Missing	1	6	
Ductal	46 (78.0%)	53 (76.8%)	
Lobular	5 (8.5%)	12 (17.4%)	
Other	8 (13.6%)	4 (5.8%)	
Tumor grade			0.46
Missing	18	26	
Grade 1	13 (31.0%)	15 (30.6%)	
Grade 2	18 (42.9%)	26 (53.1%)	
Grade 3	11 (26.2%)	8 (16.3%)	
Time from benign biopsy to breast cancer			0.22
≤5 y	24 (40.0%)	23 (30.7%)	
6–10 y	19 (31.7%)	18 (24.0%)	
11–15 y	10 (16.7%)	17 (22.7%)	
>15 y	7 (11.7%)	17 (22.7%)	
Nodal status (invasive cancers only)			0.30
Missing	5	4	
Negative	27 (69.2%)	44 (78.6%)	
Positive	12 (30.8%)	12 (21.4%)	
Tumor size (cm) (invasive cancers only)			0·46
N	41	57	
Mean (SD)	1.6 (1.1)	1.9 (1.9)	

[a]Seven cases with concomitant ADH and ALH excluded from table, and one with atypia type unspecified.
[b]*P* values calculated using χ^2 tests for categorical variables and *t* tests for continuous variables.

breast. Our observations do not support present assumptions that ADH and ALH have substantively different behaviors. More DCIS may occur in women with ADH than ALH (25% vs. 13%, $P = 0.07$), but numbers are small and this was not statistically significant. Also, in the first 5 years after atypia diagnosis, women with ADH are more likely to have an ipsilateral breast cancer than in later years. Comparing these breast cancers arising in women with a history of either ADH or ALH to breast cancers developing in the general population, the proportion of DCIS, histologic types, and distribution of grade is virtually identical in this cohort to an unselected group of breast cancers present in the Mayo Breast Cancer Tissue Core (personal communication, James N. Ingle, MD, Mayo Clinic, Rochester, MN).

Does a clear pattern emerge pointing toward atypias as direct precursors versus generalized risk indicators? In fact, there are features of both. Features supporting a precursor role include the predilection for cancers in the ipsilateral breast and at earlier time-points in follow-up. In contrast, continued risk over the long term, including contralateral events, with a typical pattern of breast cancer histologies and grades support atypia's role as a generalized risk indicator. Certainly for ADH and ALH, the tissue bed that gave rise to the atypia, namely the ipsilateral breast, is twice as likely to give rise to a later breast cancer, despite routine excision of the atypia. This same predominance of subsequent ipsilateral to contralateral disease is seen following lumpectomy alone for both noninvasive and invasive breast cancer (21, 22). This underscores the biologic relevance of atypia as a premalignant lesion or more precisely, the premalignant nature of the surrounding tissue bed. Other abnormal foci must be present that are either poised to progress to breast cancer or already possess a full malignant phenotype (i.e., occult breast cancers). Especially with the frequency of

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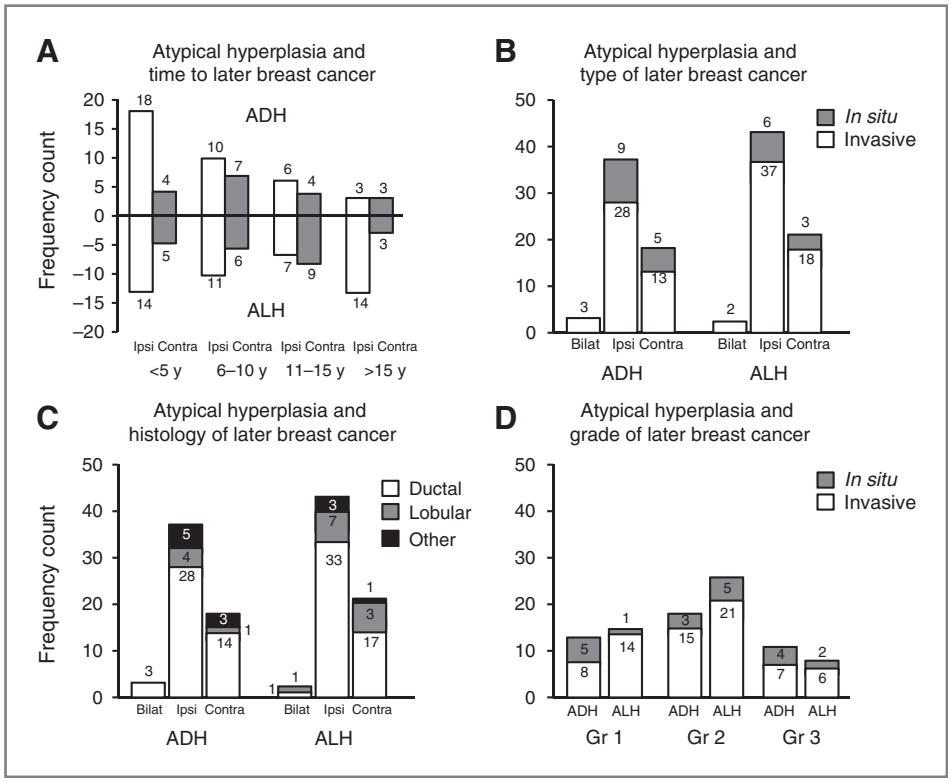

Figure 2. A, time to later breast cancer, by side of breast cancer, for women with ADH and ALH. B, type of later breast cancer for women with ADH versus ALH. Either side or type of breast cancer is missing for 2 women with ADH and 9 with ALH. C, histology of later breast cancers in women with ADH versus ALH. Note that 7 mixed ductal lobular invasive cancers are included in the invasive ductal group in women with ADH, and 9 in women with ALH. Either side or histology is missing for 2 women with ADH and 9 women with ALH. D, grade of later breast cancers in women with ADH versus ALH. Both invasive breast cancers and DCIS displayed. Either side or grade is missing for 18 women with ADH and 26 women with ALH.

ipsilateral breast cancers in the first 5 years after a diagnosis of atypia and given what is known about growth kinetics of occult tumors (23), the concomitant presence of occult breast cancers seems highly likely. As reported in the NSABP P-1 study, women with atypia who received tamoxifen experienced a 75% reduction in risk of breast cancer at 7 years of follow-up (RR = 0.25; 95% CI, 0.10–0.52), suggesting that in such early follow-up, much of the risk reduction may represent treatment of occult disease (24).

For contralateral breast cancers, or breast cancers that develop much later after the diagnosis of atypia, the increased risk may reflect a persistent microenvironmental effect across the breast tissue (25) as well as the existence of a proposed mutator phenotype (26, 27); comparison of atypical biopsies that give rise to earlier, ipsilateral cancers versus later, contralateral cancers could provide insight into these potential etiologies.

A number of recent studies have been suggested to support a model of breast cancer development in which atypia represents a nonobligate precursor lesion of low-grade DCIS and invasive disease (reviewed in refs. 8 and 28). This concept derives from both genomic and histologic observations. First, many low-grade or better prognosis DCIS and invasive breast cancer are diploid or near-diploid, and frequently contain deletions of chromosome 16q, whereas high-grade or poorer prognosis breast cancer, although generally aneuploid, only rarely have deletions of 16q (29–32). Genomic analyses of women with atypia have revealed that these lesions are generally clonal, with similar genomic alterations to those found in low-grade breast cancer, including frequent deletions of 16q (30, 33–40). Second, molecular classification methods have provided evidence that estrogen receptor (ER)-positive and ER-negative breast cancer are fundamentally different diseases, with different etiologies (reviewed in refs. 41 and 42), where lower grade and better prognosis breast cancers are generally ER-positive (in the intrinsic classification system, these usually associate with the luminal category), and higher grade/poorer prognosis breast cancers are generally ER-negative (associating with the HER2 and basal categories). That atypias are generally ER-positive (43-44) provides further circumstantial evidence for a role of atypias as a precursor or risk factor for development of lower grade/better prognosis breast cancer.

However, limitations of these models should be noted: breast cancers assigned to intrinsic subtypes still show considerable genetic heterogeneity and differences in clinical outcome (45, 46), and there is evidence that a substantial minority of cancers developing along a low-grade pathway can progress to higher grade, poorer prognosis breast cancer (11, 47). Therefore, defining methods to identify which women with atypia are likely to progress to breast cancer, as well as which of those cancers will be lower or higher grade is now an important clinical objective.

Page and colleagues have reported on a series of 252 women with ALH, 50 of whom developed invasive breast cancer, with two thirds of these cancers occurring in the same breast as the atypia (48). Our findings in ALH mirror this pattern. In addition, we show here that the same predilection for ipsilateral disease is seen in women with

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ADH. Regarding characteristics of later breast cancer, Page and colleagues reported that women with ALH tend to develop breast cancer subtypes with good prognosis (49). However, in our series, we see a predominance of invasive ductal cancers developing in women with ALH and ADH, the majority of which are moderate or high grade. In a report from the Nurses' Health Study, Jacobs and colleagues characterized the invasive breast cancers that developed in 14 women with ADH: 11 were ductal and 3 lobular/other. They also characterized 12 invasive breast cancers that developed in women with ALH, with 11 being ductal cancers and one lobular (50). Although theirs was a smaller study, the distributions of histology match those seen in our cohort.

With 327 women with ALH, our report permits more in-depth characterization of this poorly understood population. We found that women with ALH often had higher risk features than those with ADH, including more foci of atypia, younger age and less complete involution (data not shown). In terms of the breast cancers that develop in women with ALH, they are more likely to be invasive, with histologies and grade similar to what is seen in the general population of women. Thus, in our view, ALH and ADH both represent important premalignant entities.

Besides the size of this cohort, and the use of central pathology review, other strengths include information on both side and timing of subsequent breast cancers, and the completeness of follow-up for breast cancer events. A limitation is that this is a single institution study, which could reflect some bias in the findings. The women in our benign breast disease cohort come from the upper Midwest (3). Most biopsies are performed because of a concern detected during regular screening. Included here are only those women for whom atypia was found on biopsy at the Mayo Clinic. Specifically, women referred to Mayo because of a finding of atypia on an outside biopsy are not included. Although it is possible that the finding of atypia could have led to more active screening, in fact the majority of women with benign breast disease are already following annual screening recommendations. Study limitations are that certain subgroups within atypia remain small, restricting our ability to make firm conclusions throughout.

In summary, these findings underscore the importance of both ADH and ALH as premalignant lesions arising in an altered tissue bed. The affected breast is at especially high risk for breast cancer in the first 5 years after diagnosis of breast cancer, with risk remaining elevated in both breasts long term. Both ADH and ALH portend risk for DCIS and invasive breast cancers, predominantly ductal, with two thirds moderate or high grade. These longitudinal data can help to inform clinical management strategies.

Disclosure of Potential Conflicts of Interest

R. Santen has a commercial research grant from Pfizer. R. Santen is a consultant/advisory board member of Pfizer. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.C. Hartmann, M.H. Frost, D.W. Visscher, A.C. Degnim
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.C. Hartmann, M.H. Frost, R.J. Santen, R.A. Vierkant, L.L. Benetti, D.W. Visscher, A.C. Degnim
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