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ORIGINAL REPORT

Stratification of Breast Cancer Risk in Women With Atypia: A Mayo Cohort Study

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ABSTRACT

Purpose
Atypical hyperplasia is a well-recognized risk factor for breast cancer, conveying an approximately four-fold increased risk. Data regarding long-term absolute risk and factors for risk stratification are needed.

Patients and Methods
Women with atypical hyperplasia in the Mayo Benign Breast Disease Cohort were identified through pathology review. Subsequent breast cancers were identified via medical records and a questionnaire. Relative risks (RRs) were estimated using standardized incidence ratios, comparing the observed number of breast cancers with those expected based on Iowa Surveillance, Epidemiology, and End Results (SEER) data. Age, histologic factors, and family history were evaluated as risk modifiers. Plots of cumulative breast cancer incidence provided estimates of risk over time.

Results
With mean follow-up of 13.7 years, 66 breast cancers (19.9%) occurred among 331 women with atypia. RR of breast cancer with atypia was 3.88 (95% CI, 3.00 to 4.94). Marked elevations in risk were seen with multifocal atypia (eg, three or more foci with calcifications [RR, 10.35; 95% CI, 6.13 to 16.4]). RR was higher for younger women (< 45; RR, 6.76; 95% CI, 3.24 to 12.4). Risk was similar for atypical ductal and atypical lobular hyperplasia, and family history added no significant risk. Breast cancer risk remained elevated over 20 years, and the cumulative incidence approached 35% at 30 years.

Conclusion
Among women with atypical hyperplasia, multiple foci of atypia and the presence of histologic calcifications may indicate "very high risk" status (> 50% risk at 20 years). A positive family history does not further increase risk in women with atypia.

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INTRODUCTION

Atypical hyperplasia is a well-established risk factor for subsequent breast cancer. Multiple studies corroborate an approximately four-fold increased risk of breast cancer in women undergoing surgical biopsy with a finding of atypia.[1-7] Despite good concordance on the estimated relative risk (RR) with atypia, estimates of absolute risk with long-term follow-up are not well established. Reliable breast cancer risk estimates for women with atypia are crucial for risk-benefit analysis and decision making regarding risk-reduction strategies.

The Gail model in current use predicts a dramatically increased risk for those women who have both atypia and a family history (over that of atypia alone).[8] Prior published literature has stated that the risk of breast cancer abates considerably after 10 years after a diagnosis of atypia,[9] whereas more recent evidence indicates otherwise.[10] It is also unclear whether breast cancer risk is higher in cases of atypical ductal hyperplasia (ADH) versus atypical lobular hyperplasia (ALH).

Here, we present a comprehensive description of breast cancer risk in women with atypical hyperplasia, based on 331 women with atypia in the Mayo Benign Breast Disease Cohort. Our investigation addresses the effect of family history on atypia risk, the effect of time since biopsy, the influence of ductal versus lobular histology, effects of age at atypia diagnosis, and presence of calcifications on breast cancer risk. In addition, we provide absolute risk estimates over time, and we also present a new histologic feature of atypia—multifocality—that stratifies breast cancer risk among women with atypia.

PATIENTS AND METHODS

Study Population

Entry criteria for the study cohort have been previously described.[1] Briefly, this comprises an institutional review board–approved study of women ages 18 to 85 years who had a benign breast biopsy via surgical excision during 1967 to 1991. The initial cohort included 9,087 women.[1] With additional follow-up, data are now available for 9,376 women, 331 (3.5%) of whom had atypical hyperplasia.

Follow-Up

Follow-up for breast cancer events (including both invasive cancer and ductal carcinoma in situ [DCIS]) and risk-factor information were obtained for all women with atypia through the Mayo medical record and a study questionnaire. Family history was classified as negative, strong, or weak. The criteria for a strong family history were at least one first-degree relative with breast cancer before the age of 50 years or two or more relatives with breast cancer, with at least one being a first-degree relative. Any lesser degree of family history was considered weak.[1]

Histology

All available archival hematoxylin and eosin–stained sections were evaluated by our breast pathologist (D.W.V.), without knowledge of the original histologic diagnoses or patient outcomes. The number of slides reviewed per case was variable because of the retrospective nature of the study, with a mean of 3.2 (standard deviation, 3.7). Calcifications were recorded for each case when seen histologically. A diagnosis of ADH or ALH was based on the criteria of Page et al.[3,11] ADH was characterized by filling and distension of involved ducts by an architecturally complex proliferation of monotonous cells forming "punched out" (cribriform-like) secondary lumens or micropapillary formations. Although well-developed examples of ADH share some morphologic features with low-grade DCIS, the latter is characterized by tumefactive growth (requiring complete involvement of >2 contiguous lumens) as well as greater nuclear enlargement and hyperchromatism. For each example of atypical hyperplasia, the number of separate foci was defined. Multifocal atypia required its identification in more than one terminal duct lobular unit (TDLU) as defined by clear separation from another by nonspecialized interlobular mammary stroma. All cases of multifocal atypia were agreed on by two study pathologists (D.W.V. and C.A.R.).

The primary study pathologist (D.W.V.) identified 332 cases of atypia from the entire benign breast disease cohort of 9,376. To address concerns of reproducibility in the diagnosis of atypia,[12] we performed a nested study of concordance, blinding another pathologist (H.B.) to the study diagnoses in a random subset of several hundred samples from the original cohort, including nonproliferative lesions, proliferative disease without atypia, and atypical hyperplasia. Of 189 atypia samples reviewed for concordance, 165 (87.3%) atypias were similarly classified by subsequent independent review. Of the remaining 24 cases with differing interpretation, 18 were then judged to have atypia by joint review (D.W.V. and H.B.), and five of six remaining cases had atypia by review of a third "tiebreaker" breast pathologist (C.A.R.). The one case in question was excluded from further analysis, leaving a total of 331 subjects for study.

Statistical Analysis

Follow-up was defined as the number of days from benign biopsy to date of breast cancer diagnosis, death, or last contact. We estimated RRs with standardized incidence ratios (SIRs) and 95% CIs, dividing observed numbers of incident breast cancers by expected counts. We calculated expected counts by apportioning each individual's follow-up time into 5-year age and calendar-period categories, and applying these person-years to population-based incidence rates, thereby accounting for differences in these variables. 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 racial similarities compared with our cohort.[1] We extrapolated incidence-rate data for cohort follow-up occurring outside the SEER timeframe (1973-2002), such that person-years before 1973 were applied to 1973 to 1975 incidence rates, and person-years subsequent to 2002 were applied to 2001 to 2002 incidence rates. Assuming a two-sided test of hypothesis and a type I error rate of 0.05, we would have 80% power to detect SIRs as low as 3.61 if the expected event count is 2.5, as low as 2.97 if the count is 4.2, as low as 2.08 if the count is 10.3, and as low as 1.84 if the count is 17. Note that these expected counts reflect the approximate expected numbers of events in our cohort for women with three or more foci of atypia, two foci, one focus, and all subsets combined, respectively.

Recognizing that other biologic mechanisms may modify the association of atypia and breast cancer risk, we formally assessed the potential differential effects of these mechanisms using Poisson regression analyses. This approach allowed us to estimate SIRs with the flexibility that generalized linear models provide, such as covariate adjustment and tests for trend or heterogeneity across subgroups. For all analyses, the log-transformed expected event rate for each individual was modeled as the offset term.

We displayed observed and expected event rates using cumulative incidence curves and corresponding 95% confidence limits, accounting for the effects of death as a competing risk.[13] Expected events were calculated for each 1-year follow-up interval in a manner similar to that used for determining SIRs. A modified Kaplan-Meier approach was used to cumulate expected incidence over these intervals. The expected curve was then smoothed using linear interpolation.

We compared the RR of ipsilateral versus contralateral breast cancer overall and across different medical characteristics using ratios of corresponding incidence rates. When calculating incidence for ipsilateral cancer, individuals with contralateral cancer were excluded at their diagnosis date, and vice versa. Women with missing laterality, or having bilateral biopsies or cancer, were excluded for both events. The RRs are equivalent to ratios of observed events, as the approach yields identical person-years for each event type. We thus used properties of the binomial distribution to obtain exact 95% CIs for these RRs.[14] All statistical tests were postulated a priori and were two sided, and all analyses were conducted using the SAS software system (SAS Institute, Cary, NC).

RESULTS

Characteristics of Patients and Pathologic Specimens

A total of 331 women with atypia were identified in our cohort between 1967 and 1991. In Table 1, we present the patients' vital status, breast cancer status, family history, age at biopsy, year of biopsy, indication for biopsy, and histologic features. Women were likely to be older than 55 at diagnosis of atypia (55.9%), and 42.9% had a family history of breast cancer (23.5% with a strong family history). Histologic findings included calcifications in most cases of atypia (68.6%); most cases (60.1%) had only one focus of atypia. The relative percentages of women with one, two, and three or more foci of atypia remained stable over the time period of the cohort. The proportions of women with ADH and ALH were similar.

Subsequent Breast Cancer Risk and Modifying Factors

The 331 women with atypia were followed for a total of 4,543 person-years (mean 13.7 years), with 66 (19.9%) observed breast cancer events to date. The histologic types are known in 61 of these, with 53 (86.9%) of 61 invasive cancers and eight (13.1%) of 61 DCIS. The majority of invasive cancers were ductal type (47 of 53, 89%), and the remaining six invasive lobular cancers were divided between the ALH and ADH subgroups. Table 2 shows the estimated RRs for breast cancer associated with various characteristics. The overall group with atypia demonstrates a four-fold RR of breast cancer (RR, 3.88; 95% CI, 3.00 to 4.94) compared with the general population.

Family History

There were no significant differences in RR seen among the subgroups with a strong family history (RR, 3.59; 95% CI, 1.96 to

Table 1. Clinical and Histologic Characteristics Among the 331 Women With Atypical Hyperplasia From the Mayo Benign Breast Disease Cohort Study

Characteristic	No.	%
Vital status		
Deceased	101	30.5
Alive	230	69.5
Breast cancer status		
Noncase	265	80.1
Case	66	19.9
Age at biopsy, years		
Mean	58	
SD	12	
Family history of breast cancer		
Unknown	42	
None	165	57.1
Weak	56	19.4
Strong	68	23.5
Age at BBD, years		
< 45 at BBD Dx	46	13.9
45-55 at BBD Dx	100	30.2
> 55 at BBD Dx	185	55.9
Year of BBD		
1967-1971	15	4.5
1972-1976	35	10.6
1977-1981	40	12.1
1982-1986	96	29.0
1987-1991	145	43.8
Indication for biopsy		
Unknown	6	
Palpable mass	139	42.8
Mammographic abnormality	186	57.2
Calcifications		
Without calcifications	104	31.4
With calcifications	227	68.6
Histologic subtype		
Lobular	175	52.9
Ductal	142	42.9
Lobular and ductal	14	4.2
No. of foci of atypia		
1	199	60.1
2	81	24.5
≥ 3	51	15.4

Abbreviations: SD, standard deviation; BBD, benign breast disease; Dx, diagnosis.

6.03), a weak family history (RR, 5.59; 95% CI, 3.20 to 9.09), or a negative family history (RR, 3.81; 95% CI, 2.60 to 5.37; Table 2; Fig 1A).

Age at Biopsy

Women with atypia diagnosed at younger age had a higher RR compared with age-matched expected rates (Table 2; Fig 1C). The RR was 6.76 at age less than 45, 5.10 at age 45 to 55, and 2.87 at age greater than 55 years (P for trend = .01). The increased risk seen in younger women was not due to a positive family history, because there was no difference in risk for women with and without a family history in each age subgroup (data not shown).

Number of Foci of Atypia

Increasing risk was seen with increasing foci of atypia: RR = 2.33 with a single focus, 5.26 for two foci, and 7.97 for three or more foci, with a highly significant test for trend ($P < .001$; Fig 1B). The increased risk seen with multiple foci of atypia was not due to predominance of young (higher risk) women in those subgroups; women younger than 45 years constituted only 4.94% and 7.84% of the subgroups with two and three foci of atypia, compared with 19.1% of the subgroup with one focus. Multivariate Poisson regression analysis also confirmed that young age and multifocality contributed independently to increased risk.

Calcifications

Risk was dramatically increased in the small group of women (n = 38) with both calcifications and three or more foci of atypia (RR, 10.4; 95% CI, 6.13 to 16.4). However, women with calcifications and less than three foci of atypia (RR, 3.1) had risk similar to that of patients with fewer than three foci of atypia and no calcifications (RR, 3.31).

Histologic Type of Atypia

Histologic type of atypia did not affect breast cancer risk, because the RR of breast cancer was the same for ADH and ALH, although the few individuals with both histologic types may have higher risk (Fig 1D).

Indication for Biopsy

Breast cancer risk was similar whether a palpable or mammographic concern prompted the biopsy.

At-Risk Time Interval and Cumulative Incidence of Breast Cancer

The RR of breast cancer for the entire group with atypical hyperplasia was elevated persistently beyond 15 years, with a 20-year cumulative risk of 21% (95% CI, 14% to 28%) and a 25-year cumulative risk of 29% (95% CI, 20% to 38%; Fig 2). Stratification based on number of foci of atypia demonstrates a cumulative incidence of 18% for a single focus, 45% for two foci, and 48% for three or more foci of atypia at 25 years of follow-up (Fig 3).

Laterality of Breast Cancer Risk

Of the 66 women with atypia who subsequently developed breast cancer, side of cancer and side of atypia are known in 57 cases. Although cancer was more frequent in the ipsilateral breast, this difference was not statistically significant for the overall group with atypia (RR, 1.38 for ipsilateral *v* contralateral event; 95% CI, 0.79 to 2.21). However, the 32 women with atypia who developed breast cancer within 10 years of their benign biopsy were 2.2 times more likely (95% CI, 1.02 to 4.86; $P = .05$) to develop cancer in the same breast versus the opposite breast. Women with ADH had higher ipsilateral risk (RR, 1.50; 95% CI, 0.62 to 3.82), and women with three or more foci also had higher risk of ipsilateral breast cancer (RR, 2.20; 95% CI, 0.71 to 4.52), although these increases did not reach statistical significance due in part to small numbers of events and modest statistical power for these analyses. Women with ALH had similar cancer risk in both breasts (RR, 1.08; 95% CI, 0.45 to 2.14).

DISCUSSION

Having reliable breast cancer risk estimates for women with atypical hyperplasia is imperative in order to tailor their care appropriately. For women with atypia, the Gail model is the only model available for risk

Table 2. Risk Factors for Breast Cancer Among the 331 Women With Atypia From the Mayo Benign Breast Disease Cohort Study

Variable	No.	Person-Years	Observed Events	Expected Events	RR	95% CI
Overall atypia group	331	4,543	66	17.0	3.88	3.00 to 4.94
Age at benign biopsy, years						
< 45	46	678	10	1.5	6.76	3.24 to 12.40
45-55	100	1,540	26	5.1	5.10	3.33 to 7.48
< 55	185	2,325	30	10.4	2.87	1.94 to 4.10
No. of foci of atypia						
1	199	2,792	24	10.3	2.33	1.49 to 3.46
2	81	1,086	22	4.2	5.26	3.29 to 7.96
≥ 3	51	665	20	2.5	7.97	4.87 to 12.30
Calcifications						
Without	104	1,529	18	5.6	3.21	1.90 to 5.08
With	227	3,013	48	11.4	4.21	3.10 to 5.58
< 3 foci	189	2,536	30	9.7	3.10	2.09 to 4.43
≥ 3 foci	38	478	18	1.7	10.4	6.13 to 16.40
Histologic subtype						
Lobular	175	2,535	34	9.3	3.67	2.54 to 5.13
Ductal	142	1,815	27	7.0	3.83	2.53 to 5.58
Lobular and ductal	14	194	5	0.7	7.10	2.31 to 16.5
Family history of breast cancer						
None	165	2,226	32	8.4	3.81	2.60 to 5.37
Weak	56	763	16	2.9	5.59	3.20 to 9.09
Strong	68	1,029	14	3.9	3.59	1.96 to 6.03
Indication for biopsy						
Palpable mass	139	2,068	33	7.2	4.55	3.13 to 6.39
Mammographic abnormality	186	2,409	32	9.5	3.36	2.30 to 4.74

NOTE. RR and CI represent standardized incidence ratio and 95% confidence limits, comparing observed number of events to those expected based on Iowa Surveillance, Epidemiology, and End Results data. All results account for the effects of age and calendar period.
Abbreviation: RR, relative risks.

prediction.[8] In this model, calculations of risk for women with atypia and a family history are dramatically higher, based on prior evidence from the Nashville study.[2] Therefore, for a 50-year-old white woman with menarche at age 12, first birth at 24, and atypia on breast biopsy, the predicted lifetime risk of breast cancer is 17.5%. If that same woman also has a first-degree relative with

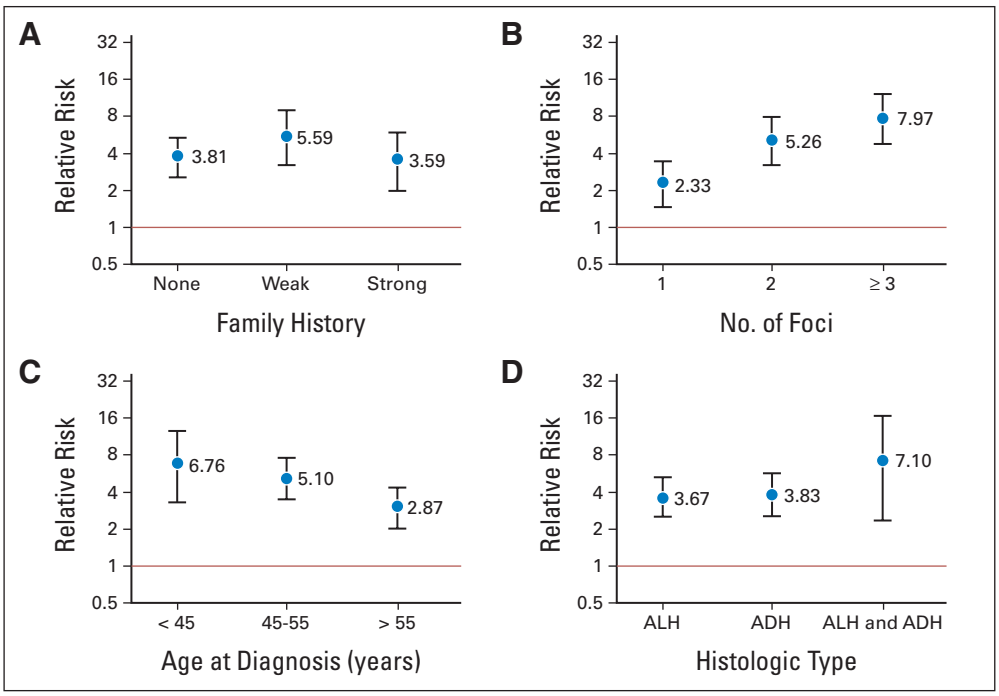

Fig 1. Stratification of breast cancer risk for women with atypical hyperplasia. (A) Family history, (B) number of foci, (C) age at diagnosis, and (D) histologic type. Relative risks expressed as standardized incidence ratios and 95% confidence limits, comparing observed number of events to those expected based on Iowa Surveillance, Epidemiology, and End Results data. All results account for the effects of age and calendar period. Horizontal lines at 1.0 reflects the overall expected relative risk in the cohort. ALH, atypical lobular hyperplasia; ADH, atypical ductal hyperplasia.

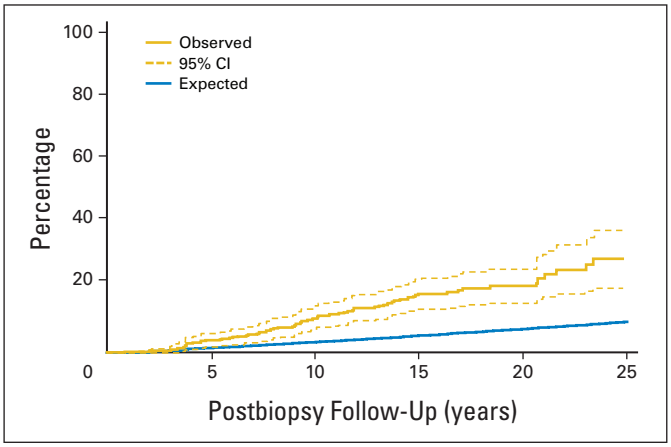

Fig 2. Cumulative risk of breast cancer over time. Observed cumulative breast cancer incidence among women with atypical hyperplasia, with 95% CIs represented by stippled lines. Expected breast cancer events were calculated by applying age- and calendar period–stratified person-years of observation to corresponding Iowa Surveillance, Epidemiology, and End Results breast cancer incidence rates. Observed and expected events cumulated after accounting for death as a competing risk.

breast cancer, her lifetime risk doubles to 34%. Our data indicate that the Gail model predicts inaccurately for such women because the increased risk of breast cancer associated with atypia is independent of the effect of family history.

Women in our cohort with atypia and a positive family history of breast cancer had no additional increased risk of breast cancer over that of atypia alone. This finding counters the commonly held view proposed by the Nashville study (ie, that atypia and a positive family history increase breast cancer risk additively). When data from other major studies of benign breast disease are considered along with the Mayo findings, the preponderance of evidence calls into question the result from the Nashville group. In that study, the subgroup of women with atypia and a family history was small (n = 39) with an RR of 8.9 (95% CI, 4.8 to 17), compared with 3.5 (95% CI, 2.3 to 5.5) in 193

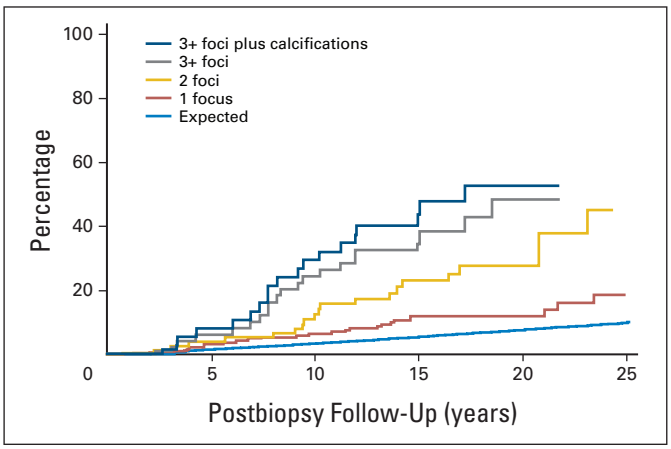

Fig 3. Observed and expected cumulative breast cancer incidence among women with atypical hyperplasia, stratified by number of foci of atypia and histologic presence of calcifications. Expected events calculated by applying age- and calendar period-stratified person-years of observation among all women with atypia to corresponding Iowa Surveillance, Epidemiology, and End Results breast cancer incidence rates. Observed and expected events cumulated after accounting for death as a competing risk.

women with atypia and no family history.[2] In contrast, evaluation of a much larger population in the Breast Cancer Detection and Demonstration Project showed similar frequencies of breast cancer in women with atypia and family history (16 of 261, 6.1%) compared with those with atypia alone (51 of 1,044, 4.9%).[4] Recent data from the Nurses' Health Study confirm our finding that a family history of breast cancer in a first-degree relative does not further increase risk among women with atypical hyperplasia.[15] To explain these findings, we postulate that atypical hyperplasia is a phenotype reflecting increased risk; this phenotype derives from both inherited risk and lifetime exposures. Thus, the histologic presence of atypia already reflects the increased breast cancer risk inherent in a positive family history.

We have identified a new histologic variable that appears to stratify risk in women with atypia: multifocality. The RR of breast cancer increases in a dose-response fashion for women with one, two, and three or more foci of atypia, with a statistically significant test for trend. With a single focus, the cumulative incidence of breast cancer reached 18% at 25 years. For women with two or more foci of atypia, the cumulative risk of breast cancer was greater than 40% at 25 years. Moreover, in the highest risk subgroup of women with three or more foci and histologic calcifications, the cumulative incidence exceeded 50% over 25 years. This level of risk approaches that reported for carriers of BRCA mutations.[16] In line with our observation, differential risk based on extent of disease has been established for lobular neoplasia (ie, ALH *v* lobular carcinoma),[17] and the number of foci of atypia found in core needle biopsy specimens correlates with the likelihood of finding cancer at surgical excision.[18]

Some may question whether multifocal atypias may actually represent subtle in situ carcinoma, particularly those of the ADH type. In cases of multifocal ADH, it should be emphasized that individual foci arose in separate and distinct terminal duct lobular units, none of which measured more than 2 mm. Hence, these examples failed to exhibit the confluent degree of cellular proliferation requisite for a diagnosis of DCIS. We submit that more widespread distribution of atypical foci within breast tissue signals a larger burden of at-risk tissue that has progressed along the continuum toward breast cancer. The data presented in this article provide evidence that the extent of premalignant breast change is related to subsequent cancer risk. Since this is the first report of the clinical relevance of this histologic finding, we recognize the need for validation and plan to evaluate this factor in a more recent cohort from our institution. Furthermore, we hope that other research groups with large numbers of patients with atypical hyperplasia will also examine the relevance of multifocal atypia in their study sets.

Age at the diagnosis of atypia also emerged as a significant modifier of subsequent breast cancer risk, with a higher RR in younger women. The Nurses Health Study[6] and the Breast Cancer Detection and Demonstration Project[4] have also shown higher risk in younger women with atypia. In our cohort, this increased risk in younger women is not explained by more frequent multifocal disease or a positive family history. Perhaps atypical hyperplasia present at a young age is the result of previous oncogenic events; alternatively, breast tissue with atypia may be unusually susceptible to proposed oncogenic estrogen metabolites associated with the premenopausal hormonal environment.[19]

When counseling women with atypical hyperplasia, the length of time at risk is a key element in planning risk-reduction strategies. Dupont and Page[9] reported that the greatest risk of breast cancer after

a diagnosis of atypia lies in the first 10 years, with subsequent RR reduced by half ($P = .06$). By contrast, the Nurses Health Study[10] found that risk does not decrease over time, with RR slightly higher more than 10 years after biopsy (RR, 3.6) compared with the first 10 years (RR, 3.2). Our data confirm that the RR for breast cancer after a biopsy demonstrating atypia remains significantly elevated for at least 15 years.

Data on long-term absolute risk are more useful than RR estimates when counseling patients. Our study provides estimates of absolute risk for women with atypia and indicates a higher cumulative incidence of breast cancer with long-term follow-up than has been reported by other studies. Figures from the study of Dupont and Page show a cumulative breast cancer incidence of 13% at 20 years and 23% at 25 years in women with atypia.[9] The cumulative incidences identified in our cohort were higher: 21% at 20 years and 29% at 25 years. One factor contributing to this difference is our inclusion of DCIS as a recordable breast cancer event, whereas the Nashville study counted only cases of invasive breast cancer.[2] Because DCIS currently receives local treatment (and in some cases, systemic treatment) similar to that for early-stage invasive breast cancer, it is reasonable to include cases of DCIS when estimating risk.

Our data on the laterality of subsequent breast cancer do not allow conclusions regarding atypical hyperplasia acting as a precursor lesion, yet there is a suggestion of predilection for the ipsilateral breast that requires ongoing study. Breast cancers occurring in the first 10 years after atypia diagnosis were significantly more likely to occur in the ipsilateral breast. A recent study of gene expression profiling identified remarkably similar alterations in gene expression among ADH, DCIS, and invasive cancers found in the same specimen, supporting the role of atypical hyperplasia as a precursor lesion.[20] Regarding differences in ipsilateral risk for ductal versus lobular atypia, we found that risk was equal for both breasts after a diagnosis of ALH, which is consistent with the distribution of invasive breast cancers after a diagnosis of lobular carcinoma in situ.[21] In contrast, ADH was more likely associated with a later ipsilateral breast cancer, as has been shown for DCIS untreated after diagnostic biopsy.[22]

In conclusion, our study provides a comprehensive analysis of breast cancer risk associated with atypical hyperplasia. These findings confirm a four-fold RR of subsequent breast cancer in women with atypical hyperplasia. We estimate that the long-term absolute risk of subsequent breast cancer (in situ or invasive) is higher than previously reported—at least 25% at 25 years, and as high as 50% to 60% in a high-risk subgroup defined by multifocality and calcifications. A positive family history does not confer significantly increased risk in women with atypia. Improved risk prediction and stratification is now possible to guide risk-reduction counseling for women with atypical hyperplasia.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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