Risk of Breast Cancer Associated with Atypical Hyperplasia of Lobular and Ductal Types

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Abstract

Epidemiological studies using the histological classification of Page for benign breast disease consistently demonstrate a positive association between atypical hyperplasia and the subsequent development of breast cancer. However, atypical hyperplasia is of either lobular or ductal types, and breast cancer risk in relation to type of atypical hyperplasia has not been studied extensively. Thus, we investigated prospectively the risk of breast cancer associated with histological subtypes of benign proliferative breast disease, including the types of atypical hyperplasia, among participants in the Nurses’ Health Study who had biopsy-confirmed benign breast disease. Women who subsequently developed breast cancer were matched by year of birth and year of biopsy to participants who were free from breast cancer. Benign biopsy slides were classified according to the criteria of Page. Odds ratios (ORs) of breast cancer and 95% confidence intervals (CIs), adjusted for the matching variables and other breast cancer risk factors, were computed using unconditional logistic regression with benign nonproliferative breast disease as the referent group. Atypical ductal hyperplasia (OR = 2.4; 95% CI, 1.3–4.5) or atypical lobular hyperplasia (OR = 5.3; 95% CI, 2.7–10.4) in a prior biopsy were associated with increased breast cancer risk. Atypical lobular hyperplasia was more strongly associated with the risk of premenopausal breast cancer (OR = 9.6; 95% CI, 3.3–27.8) than with the risk of postmenopausal breast cancer (OR = 3.7; 95% CI, 1.3–10.2). The association of atypical ductal hyperplasia and breast cancer risk varied little by menopausal status. The magnitude of breast cancer risk seems to vary according to the type of atypical hyperplasia present at biopsy.

Introduction

Based on the benign breast disease classification of Page et al. (1, 2), which was endorsed by the College of American Pathologists (3), previous reports (2, 4–6) indicate that atypical hyperplasia is strongly associated with the subsequent development of breast cancer. However, atypical hyperplasia is comprised of both ductal and lobular types, and breast cancer risk associated with the types of atypical hyperplasia has not been studied in detail (1, 7). In their first report, Page et al. (7) observed that atypical lobular hyperplasia but not atypical ductal hyperplasia was associated with increased breast cancer risk. However, in a later study in which a more strict definition of atypical ductal hyperplasia was used, Page et al. (1) observed that both types of atypical hyperplasia were associated with an elevated risk of subsequent invasive breast cancer. Since these two reports, no epidemiological studies using these diagnostic criteria (1) have evaluated the associations of breast cancer risk with type of atypical hyperplasia. Thus, further study of atypical lesions in a different population would enhance our understanding of the role of these lesions in subsequent breast cancer development.

The biological meaning of atypical lobular and atypical ductal lesions is controversial (1, 8), primarily because their natural history is unclear. A central issue is whether these atypical lesions are markers of general breast cancer risk or are precursor lesions. Most studies that examined the laterality of the benign and subsequent malignant lesions (1, 4, 9) have demonstrated that only about half of the invasive breast cancers arise in the same breast in which atypical hyperplasia was previously diagnosed, suggesting that these lesions are markers of generalized risk. This observation also seems to hold for type of atypical hyperplasia, although the data are limited (1, 9).

To address these issues, we examined the association between breast cancer risk and type of atypical hyperplasia, classified according to the criteria of Page et al. (1, 2). Among women who developed invasive breast cancer, we quantified information on the laterality of both the benign and subsequent malignant lesions. This study, conducted prospectively in the Nurses’ Health Study, updates an earlier report (5) with 53 new breast cancer cases identified during 2 additional years of follow-up.

Materials and Methods

Study Population. The Nurses’ Health Study began in 1976 when 121,700 female registered United States nurses ages 30–55 years completed mailed questionnaires about known and suspected risk factors for breast cancer. Participants update this information on new questionnaires every 2 years. On all questionnaires, we inquired about benign breast disease either requiring hospitalization or diagnosed at biopsy. For this investigation, par-
participants were drawn from women who were free from diagnosed breast cancer in 1976 and who reported on the 1976 or later questionnaires a history of benign breast disease requiring hospitalization or biopsy. The details of follow-up, ascertainment of cases and controls, and benign breast disease slide review from 1976 through 1986 were described previously (5). We used the same protocol for ascertainment of cases and controls for the 1988 follow-up period, and this is summarized below.

Identification of Breast Cancer Cases and Controls. Potential cases were women who reported a new diagnosis of either invasive or in situ breast cancer after 1976 and after a previous diagnosis of biopsy-confirmed benign breast disease. Self-reported breast cancers were confirmed by review of pathology reports. For each breast cancer case, three to four potential controls were selected randomly from among participants who were born in the same year, reported a first hospitalization or biopsy for benign breast disease in the same year, and remained free from breast cancer at the time the case was diagnosed. We asked all eligible cases and controls for written permission to obtain slides from their first biopsy and considered the return of a signed medical records release form to constitute informed consent. This protocol was approved by the Institutional Review Board of the Brigham and Women’s Hospital.

On the 1988 questionnaire, 141 participants with a history of benign breast disease reported a first diagnosis of breast cancer. These potential cases were matched to 494 potential controls. We were able to contact 140 cases (99.3%) and 467 controls (94.5%). Of these, seven cases (5.0%) and nine (1.9%) controls denied a previous diagnosis of benign breast disease. Two other controls were deceased. Of the remaining 133 cases and 456 controls who confirmed a diagnosis of benign breast disease, 123 cases (92.5%) and 414 potential controls (90.8%) gave permission for us to examine their biopsy slides. Slides from the first biopsy were unavailable for 54 cases (43.9%) and 196 controls (47.3%). Among these 250 participants, slides were missing for (a) 38 (70.4%) cases and 138 (70.4%) controls because the biopsy had occurred sufficiently long ago that the hospital had destroyed the slides; (b) 3 (5.6%) cases and 32 (16.3%) controls because the hospital did not respond to our repeated inquiries; (c) 9 (16.7%) cases and 15 (7.7%) controls because the hospital had no record of the patient or of the biopsy; and (d) 4 (7.4%) cases and 11 (5.6%) of the controls because of other miscellaneous reasons.

We were able to obtain material from the hospitals for 69 cases and 218 controls. However, for 8 cases and 16 controls, the specimen was from a cyst aspiration, and for 10 cases and 218 controls. However, for 8 cases and 16 controls, the tissue did not represent benign breast disease or breast tissue. Ten controls were excluded because their first biopsy occurred less than 6 months before the breast cancer diagnosis date of the matched case. Thus, 51 cases (38.3%) and 191 controls (41.9%) who confirmed a first benign breast biopsy had slides available for analysis.

In addition, slides from 2 cases and 3 controls whose permission forms we received after the close of the 1986 follow-up period [on which the previous report (5) of 121 cases and 488 controls was based] were also available for analysis. Thus, the current study is based on the centralized review of benign breast biopsy slides for 174 cases and 682 controls.

Exposure Assessment. A total of 33 histological features were characterized for each benign biopsy specimen. Based upon these features, biopsies were classified by one of two breast pathologists (J. L. C. and S. J. S.) according to the criteria of Page et al. (1, 2) into one of three histological subtypes of benign breast disease: nonproliferative, proliferative without atypia, or atypical hyperplasia. All specimens with possible or definite atypical hyperplasia were reviewed jointly by the pathologists. Biopsies, including bilateral biopsies, were classified according to the most severe changes present. To ensure that the exposure categories were mutually exclusive, we classified biopsies with both atypical ductal and atypical lobular hyperplasia (seven cases and seven controls) as having atypical lobular hyperplasia. The pathologists were unaware of whether the slides were from a case or a control.

In the previous report in this cohort (5), the category of nonproliferative disease included fibroadenoma and fibroadenomatous change as well as duct ectasia, apocrine metaplasia, and mild hyperplasia. Recently, however, Dupont et al. (10) observed an increased risk of breast cancer among women with nonproliferative benign breast disease with fibroadenoma compared to women without fibroadenoma. In accord with this observation, we have now classified fibroadenoma and fibroadenomatous change as proliferative disease without atypia, a category that also includes intraductal papilloma, radial scar, sclerosing adenosis, and moderate or florid ductal hyperplasia. The definition of atypical hyperplasia remains unchanged from the previous analysis and includes atypical ductal and lobular hyperplasias (1).

Covariate Information. At baseline in 1976, we asked about age at menarche, number of pregnancies, age at first birth, and menopausal status. Menopause status, parity (at least one pregnancy of ≥6 months), and history of breast cancer among mothers and sisters were also ascertained from the biennial follow-up questionnaires. A case was classified according to her responses on the questionnaire completed just before her breast cancer diagnosis. For each control, we assigned as an index date the date of breast cancer diagnosis of the matched case. Covariate information for the control was classified according to the level reported on the questionnaire completed just before the index date.

Data Analysis. The RR\(^3\) of breast cancer among women with proliferative disease without atypia or with atypical hyperplasia compared to women with nonproliferative benign breast disease was estimated by the OR, which was computed using unconditional logistic regression with SAS software (11). Initially, we compared the ORs as estimated by conditional logistic regression (12) and by unconditional logistic regression (11) in which the matching factors were grouped into levels that were similar in regard to breast cancer risk (13). In these initial analyses, the ORs from conditional and unconditional logistic models were nearly identical. Thus, we report the results from unconditional logistic regression models adjusted for the matching factors and other covariates because this analytic method enabled us to use all cases and controls for whom we had historical information. The matching factors, age at breast cancer diagnosis or index date and year of biopsy, and other covariates, including age at menarche, menopause status, parity, and family history of breast cancer, were modeled as indicator variables (refer to the footnotes in each table for the categorization of these variables). To adjust parity for age at first birth among parous women while including nulliparity in the model, age at first birth was multiplied by the dummy variable for parity (0, 1) and fit as a continuous term. The \(P\) reported for the test of a difference between ORs is two-sided.

Analyses stratified by menopause status do not include 15 cases (8.6%) and 82 controls (11.9%) with unknown menopause status. Interaction between menopause and benign breast disease

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\(^3\) The abbreviations used are: RR, relative risk; OR, odds ratio; CI, confidence interval.
was modeled using indicator variables for the cross products of menopause status and each histological subtype. The statistical significance of the interaction terms was assessed by the likelihood ratio test (13). In the analysis of proportions of invasive breast cancer developing in the previously biopsied breast, we excluded women without information about which breast was biopsied or contained the malignancy (n = 31) or who had bilateral biopsies or bilateral breast cancer (n = 16). Exact 95% CIs for binomial proportions were obtained from published scientific tables (14). Fisher’s exact method (15) was used to determine whether the proportion of ipsilateral invasive breast cancer arising after a diagnosis of atypical lobular hyperplasia was greater than the proportion occurring after a diagnosis of atypical ductal hyperplasia. A two-sided P was computed.

Results

The new definition for proliferative disease without atypia resulted in the reclassification of 13 cases and 53 controls who had been in the nonproliferative category in the previous analysis (5). Among the benign breast biopsies from all cases in this investigation, 46 (26%) were classified as having nonproliferative disease, 88 (51%) were classified as having proliferative disease without atypia, and 40 (23%) were classified as having atypical hyperplasia. The distribution of benign breast histopathology among the controls was 284 (42%), 319 (47%), and 79 (12%) for nonproliferative lesions, proliferative lesions without atypia, and atypical hyperplasia, respectively (Table 1). Among those with atypical hyperplasia, 22 (55%) cases and 27 (34%) controls were classified as having atypical lobular hyperplasia, and 18 (45%) cases and 52 (66%) controls were classified as having atypical ductal hyperplasia. The median age at first benign breast disease biopsy was 43 years for both the cases and the controls. The median time since the first biopsy occurred was 10 years for the cases and the controls. The multivariate-adjusted OR of breast cancer risk among women with proliferative disease without atypia compared to women with nonproliferative disease was 1.7 (95% CI, 1.2–2.6), and the OR of breast cancer among women with atypia was 3.4 (95% CI, 2.0–5.9; Table 1). Breast cancer risk was further evaluated in relation to the type of atypical hyperplasia compared to nonproliferative disease. The risk of subsequent breast cancer was increased among women with atypical ductal hyperplasia (OR = 2.4; 95% CI, 1.3–4.5) but was more substantially elevated among those with atypical lobular hyperplasia (OR = 5.3; 95% CI, 2.7–10.4). The difference between these ORs (2.4 and 5.3) was of borderline statistical significance (P = 0.05). When the 28 breast cancer cases with carcinoma in situ were excluded from the analysis, the ORs for each histological subtype of benign breast disease changed little. Therefore, subsequent analyses included all cancer cases.

Because breast cancer risk varies according to menopausal status, we examined the associations between the subtypes of benign breast disease and breast cancer risk according to menopause status at breast cancer diagnosis or index date (83% of the cases and 81% of the controls were premenopausal at their first benign breast disease biopsy). The risk of pre- and postmenopausal breast cancer was the same (OR = 1.8) in relation to proliferative disease without atypia compared to women of the same menopausal status with nonproliferative disease (Table 2). In contrast, the risk of breast cancer associated with atypical hyperplasia seemed to differ according to menopausal status, with atypical hyperplasia more strongly related to the development of premenopausal breast cancer than to the development of postmenopausal cancer. The interaction between menopausal status and the three main histological classifications of benign breast disease, however, was not statistically significant (P = 0.59).

Breast cancer risk in relation to type of atypical hyperplasia also appeared to differ by menopausal status (Table 2). Women with atypical lobular hyperplasia were at increased risk of developing both pre- and postmenopausal breast cancers, but the association was greatest for premenopausal breast cancer. In contrast, breast cancer risk in relation to atypical ductal hyperplasia was similarly elevated in each menopause category. The risk of breast cancer associated with the histological subtypes of benign breast disease relative to those with nonproliferative lesions was assessed according to years since first benign breast biopsy (Table 3). Breast cancer risk remained elevated over time, among both women with proliferative lesions without atypia and women with atypical hyperplasia. The increase in breast cancer risk associated with atypical lobular hyperplasia was similar within each category of time since first biopsy. In contrast, there was a suggestion that breast cancer risk among those with atypical ductal hyperplasia appeared to rise with time since first biopsy.

The proportion of invasive breast cancers arising in the biopsied breast among 99 cases who had a unilateral benign biopsy is shown in Table 4. Overall, ipsilateral breast cancer occurred in 51 (51.5%) of the 99 cases. Within each category of benign breast disease, the proportion of subsequent ipsilateral cancers was not significantly different from the overall proportion. Although women with atypical lobular hyperplasia had a slightly higher proportion of ipsilateral invasive breast cancers than those with atypical ductal hyperplasia, the proportion was not significantly greater (Fisher’s exact P = 0.69).

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**Table 1** Risk of breast cancer in relation to histological subtype of benign breast disease among participants with a prior breast biopsy, Nurses’ Health Study 1976–1988

<table>
<thead>
<tr>
<th>Category of benign breast histology</th>
<th>Controls</th>
<th>Cases</th>
<th>OR*</th>
<th>Multivariate OR* (95% CI)</th>
<th>Cases</th>
<th>OR*</th>
<th>Multivariate OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonproliferative*</td>
<td>284</td>
<td>46</td>
<td>1.0</td>
<td>1.0</td>
<td>36</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Proliferative</td>
<td>319</td>
<td>88</td>
<td>1.8</td>
<td>1.7 (1.2–2.6)</td>
<td>79</td>
<td>2.0</td>
<td>2.0 (1.3–3.1)</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>79</td>
<td>40</td>
<td>3.5</td>
<td>3.4 (2.0–5.9)</td>
<td>31</td>
<td>3.6</td>
<td>3.4 (1.9–6.0)</td>
</tr>
<tr>
<td>Lobular</td>
<td>27</td>
<td>22</td>
<td>5.9</td>
<td>5.3 (2.7–10.4)</td>
<td>17</td>
<td>5.9</td>
<td>5.2 (2.5–10.9)</td>
</tr>
<tr>
<td>Ductal</td>
<td>52</td>
<td>18</td>
<td>2.4</td>
<td>2.4 (1.3–4.5)</td>
<td>14</td>
<td>2.4</td>
<td>2.4 (1.2–4.9)</td>
</tr>
</tbody>
</table>

*a OR adjusted for the matching factors: age at diagnosis (≤44, 45–54, ≥55 years) and year of benign breast disease biopsy (1948–1959, 1960–1979, 1980–1989). b ORs and 95% CIs adjusted additionally for family history of breast cancer (yes, no), age at menarche (11, 12–13, ≥14 years), menopausal status (premenopausal, postmenopausal), age at first birth, and parity (0, ≥1).

Referent category for all ORs.
Table 2  Risk of breast cancer according to histological subtype of benign breast disease within categories of menopausal status,∗ Nurses’ Health Study 1976–1988

<table>
<thead>
<tr>
<th>Category of benign breast histology</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases Controls Multivariate OR∗ (95% CI)</td>
<td>Cases Controls Multivariate OR∗ (95% CI)</td>
</tr>
<tr>
<td>Nonproliferative†</td>
<td>23 128 1.0</td>
<td>20 127 1.0</td>
</tr>
<tr>
<td>Proliferative</td>
<td>36 127 1.8 (1.0–3.2)</td>
<td>45 146 1.8 (1.0–3.4)</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>17 26 4.6 (2.1–10.4)</td>
<td>18 46 2.6 (1.2–5.6)</td>
</tr>
<tr>
<td>Lobular</td>
<td>11 9 9.6 (3.3–27.8)</td>
<td>9 16 3.7 (1.3–10.2)</td>
</tr>
<tr>
<td>Ductal</td>
<td>6 17 2.4 (0.8–6.9)</td>
<td>9 30 2.0 (0.8–5.1)</td>
</tr>
</tbody>
</table>

∗ Menopausal status at the time of breast cancer diagnosis for the cases or the index date for the controls.
† ORs and 95% CIs adjusted for age at diagnosis (≤49, 50–54, ≥55 years), year of benign breast disease hospitalization or biopsy (1948–1959, 1960–1969, 1970–1979, 1980–1989), family history of breast cancer (yes, no), age at menarche (≤11, 12–13, ≥14 years), age at first birth, and parity (0, ≥1).
‡ ORs and 95% CIs adjusted for age at diagnosis (≥54, ≥55 years), year of benign breast disease hospitalization or biopsy (1948–1959, 1960–1969, 1970–1979, 1980–1989), family history of breast cancer, age at menarche, age at first birth, and parity as listed above.
§ Referent category for all ORs.

Table 3  Risk of breast cancer according to histological subtype of benign breast disease within categories of time between first biopsy and breast cancer diagnosis, Nurses’ Health Study 1976–1988

<table>
<thead>
<tr>
<th>Category of benign breast histology</th>
<th>Years since first benign breast biopsy</th>
<th>Cases Controls Multivariate OR∗ (95% CI)</th>
<th>Cases Controls Multivariate OR∗ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤9 yrs</td>
<td>≥10 yrs</td>
<td></td>
</tr>
<tr>
<td>Nonproliferative†</td>
<td>20 156 1.0</td>
<td>26 128 1.0</td>
<td></td>
</tr>
<tr>
<td>Proliferative</td>
<td>44 178 1.9 (1.0–3.4)</td>
<td>44 141 1.6 (0.9–2.7)</td>
<td></td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>23 55 3.2 (1.6–6.4)</td>
<td>17 24 3.6 (1.6–8.2)</td>
<td></td>
</tr>
<tr>
<td>Lobular</td>
<td>15 20 5.6 (2.4–13.2)</td>
<td>7 7 5.2 (1.5–17.4)</td>
<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>8 35 1.8 (0.7–4.6)</td>
<td>10 17 3.0 (1.2–7.8)</td>
<td></td>
</tr>
</tbody>
</table>

∗ ORs and 95% CIs adjusted for age at diagnosis (≤44, 45–54, ≥55 years), year of benign breast disease hospitalization or biopsy (1948–1959, 1960–1969, 1970–1979, 1980–1989), family history of breast cancer (yes, no), menopausal status (premenopausal, postmenopausal), age at menarche (≤11, 12–13, ≥14 years), age at first birth, and parity (0, ≥1).
‡ ORs and 95% CIs adjusted age at diagnosis (≤54, ≥55 years), year of benign breast disease hospitalization or biopsy (1948–1959, 1960–1969, 1970–1979), family history of breast cancer, menopausal status, age at menarche, age at first birth, and parity as listed above.
§ Referent category for all ORs.

Table 4  Proportion of cases with a benign breast disease biopsy and subsequent invasive breast cancer in the same breast among cases for whom laterality information was available, Nurses’ Health Study 1976–1988

| Category of benign breast disease | Cases Subsequent invasive breast cancer in the biopsied breast Percentage (95% CI) Exact 95% CI |
|----------------------------------|-----------------|---------------------------------|
| Nonproliferative†                | 25 14 56.0 34.9–75.6 |  |
| Proliferative                    | 52 24 46.1 32.2–60.5 |  |
| Atypical hyperplasia             | 22 13 59.1 36.4–79.3 |  |
| Lobular                          | 11 7 63.6 30.8–89.1 |  |
| Ductal                           | 11 6 54.5 23.4–83.3 |  |

Discussion

In this prospective study of benign breast disease and breast cancer risk, proliferative lesions with or without atypia were positively associated with breast cancer risk, but breast cancer risk seemed to be more strongly associated with atypical lobular hyperplasia than with atypical ductal hyperplasia. Our results were not materially altered by reclassifying women with fibroadenoma and fibroadenomatous change from the nonproliferative disease category to the proliferative disease without atypia category. These data provide reassurance that the effect of changing the referent category in previous studies (2, 4–6) would be minimal. We also observed no substantial changes in breast cancer risk when cases with carcinoma in situ were excluded.

Others using Page’s histological classifications (1, 2) have reported RRs of breast cancer ranging from 1.3 (4, 6) to 1.9 (2) for proliferative disease without atypia and from 4.3 (6) to 5.3 (2) to 13 (4) for atypical hyperplasia. In a previous study among women in this cohort (5), the OR for breast cancer associated with proliferative disease without atypia was 1.7, and the OR associated with atypical hyperplasia was 3.4.

In their initial study of breast cancer in relation to type of atypical hyperplasia, Page et al. (7) identified four new breast cancer cases among women with a history of atypical lobular hyperplasia and two new cases among those with a history of atypical ductal hyperplasia during 3 years of follow-up. They reported that the RR of breast cancer associated with atypical lobular hyperplasia was 4.2 compared to women in the general population, but they observed no association between breast cancer risk and atypical ductal hyperplasia. Our study is more directly comparable to another cohort study conducted by Page et al. (1). In that study, during which follow-up averaged 17.5 years/participant, 16 and 18 new breast cancers were observed among women with 1 or more previous biopsies showing atypical lobular hyperplasia or atypical ductal hyperplasia, respectively. Page et al. (1) reported that compared to women with nonproliferative benign breast disease, the RRs of breast cancer were 5.8 (95% CI, 3.0–11) in relation to atypical lobular hyperplasia and 4.7 (95% CI, 2.5–8.9) in relation to atypical ductal hyperplasia. Whereas the OR of breast cancer associated with atypical lobular hyperplasia that we observed is comparable to that observed by Page et al. (1), the OR of breast cancer associated with atypical ductal hyperplasia that we observed is...
lower. Because our data suggest that breast cancer risk associated with atypical ductal hyperplasia was greater among women whose biopsy occurred 10 or more years in the past, the shorter duration of follow-up in our cohort and the evaluation of only the first benign biopsy provides one possible explanation for this apparent discrepancy.

Our results suggest that the onset of menopause after a diagnosis of atypical hyperplasia may alter breast cancer risk. As in the earlier report among women in this cohort (5), we observed that the association between atypical hyperplasia and risk of premenopausal breast cancer was considerably greater than the association with postmenopausal breast cancer. Although not directly comparable, our results are similar to those reported by Dupont et al. (6), who classified menopause status at the time of the benign breast biopsy and observed that the association between atypical hyperplasia and invasive breast cancer seemed to be stronger if the patient was premenopausal at biopsy than if she was postmenopausal. In our data, the risk of premenopausal breast cancer associated with atypical lobular hyperplasia was also greater than the risk of postmenopausal breast cancer, whereas breast cancer risk associated with atypical ductal hyperplasia did not vary by menopause status.

The observation of Page et al. (1) regarding the distributions of atypical lobular and atypical ductal hyperplasia as a proportion of all biopsies supports this variation in risk of pre-and postmenopausal breast cancer. They reported that the frequency of atypical lobular hyperplasia peaked among women ages 46–55 years and declined thereafter in the postmenopausal years, whereas the frequency of atypical ductal hyperplasia increased with age, suggesting that atypical lobular hyperplasia may be influenced by ovarian function. Nonetheless, the potential modifying effect of menopausal status on the associations between type of atypia and breast cancer risk should be interpreted cautiously because these results are based on small numbers of women with atypical lesions in each menopause category.

Our finding that the risk of breast cancer associated with atypical hyperplasia does not diminish with time since biopsy is consistent with our earlier report (5) but contrasts somewhat with that of Dupont and Page (16). They observed that breast cancer risk was greatest in the first 10 years after biopsy (RR = 9.8) but declined 11 or more years after biopsy (RR = 3.6). In our data, breast cancer risk associated with atypical ductal hyperplasia but not with atypical lobular hyperplasia appeared to rise with increasing time since biopsy, although the small numbers of cases in each time stratum resulted in unstable estimates. Despite some differences, these studies suggest that breast cancer risk associated with the types of atypical hyperplasia persists.

In studies with information about the laterality of the benign and subsequent malignant lesions, the site of invasive breast cancer was observed to be ipsilateral in 69% (1) and 58% (9) of women with atypical lobular hyperplasia and in 56% (1) and 50% (9) of women with atypical ductal hyperplasia. As with our results, these differences were not significantly different (9). The consistency of these data suggests that breast cancer risk associated with type of atypical hyperplasia is bilateral.

The main limitation of this study is the lack of available benign breast biopsy slides for a substantial proportion of the participants who gave permission to obtain them. However, as we noted above, the proportion of slides missing for cases and controls was similar (44 and 47%), and the predominant reason for missing slides, which was the routine disposal of biopsy material by the hospitals before a certain date, did not differ according to breast cancer status. Therefore, it is unlikely that the associations we observed result from selection bias.

Our results confirm previous observations that women with atypical hyperplasia are at increased risk of breast cancer and demonstrate the potential additional importance of distinguishing between atypical lobular and atypical ductal hyperplasia. Risk associated with each type of atypical lesion seemed to be independent of time since first biopsy and was bilateral, supporting the argument that these atypical lesions are markers of generalized breast cancer risk (1, 8). The persistent elevation in breast cancer risk associated with each type of atypical hyperplasia underscores the importance of continued screening after the first benign breast biopsy among women with these high-risk lesions. Further study of the natural history of atypical lobular and atypical ductal hyperplasia would clarify their role in breast carcinoma.

Acknowledgments

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Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types.


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