Benign Breast Biopsy Diagnosis and Subsequent Risk of Breast Cancer

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Abstract

Background: We examine benign breast biopsy diagnoses as reported by community pathologists in New Mexico and investigate associations with future breast cancer development.

Methods: Using data collected between 1992 and 2000 by the New Mexico Mammography Project and cancer data through 2003 from the New Mexico Tumor Registry, we calculated breast cancer rates following 14,602 benign breast biopsies for women ages 30 to 89 years. For comparison, we also calculated the breast cancer rate following 215,283 normal screening mammograms. Hazard ratios (HR) are presented.

Results: We identified 480 subsequent breast cancer diagnoses among 14,602 women with benign breast biopsies and 4,402 breast cancer diagnoses among 215,283 women with mammograms assigned a “negative” or “benign finding” assessment. Histologic diagnoses in absence of atypia had an age-adjusted HR of 1.95 [95% confidence interval (95% CI), 1.77-2.15]. Among low-risk histologic diagnoses, the strongest associations with subsequent breast cancer development included adenosis, apocrine metaplasia, calcifications, and ductal hyperplasia. Fibroadenoma, inflammation, and cysts did not exhibit an association with breast cancer development.

Conclusions: The observed breast cancer occurrence contributes to evidence of increased risk following benign biopsy. The risk associated with histologic diagnoses in absence of atypia was twice the risk experienced by women with normal mammogram evaluations and may be modified by breast density.

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Introduction

Benign histologic diagnoses of breast biopsies are common and have been associated with future development of breast cancer. Various pathologies are classified as benign, and although the risk increase associated with atypical hyperplasia has been well established (1-6), more prevalent histologic diagnoses have not been as extensively evaluated. The Cancer Committee of the College of American Pathologists updated their 1985 Consensus statement in 1998, classifying ductal carcinoma in situ, lobular carcinoma in situ, and atypical hyperplasia as marked or moderate risk factors for future development of invasive breast cancer, whereas the remaining lesions were classified as either slight or non risk factors (7, 8). However, Wang et al. (9) reported a statistically significant increased risk associated with these lower category lesions from the National Surgical Adjuvant Breast and Bowel Project’s Breast Cancer Prevention Trial. Hartmann et al. reported findings from the Mayo Clinic suggesting increased risk persisting for at least 25 years for women diagnosed with benign breast disease, in contrast to earlier findings (10, 11), although no increased risk was found specifically for women with no family history and nonproliferative findings (12).

Commonly diagnosed histologic features include adenosis, apocrine metaplasia, calcifications, cysts, fibroadenomas, fibrocystic changes, fibroses, ductal hyperplasia, and inflammation. Although a few studies (1, 3, 13-21) have investigated some of these histologic diagnoses, the degree of risk association has not been as well established, and there is need to confirm the significance of these diagnoses when made by community pathologists.

To address these questions, we examined clinical pathology reports collected in New Mexico for 14,602 women with benign breast diagnoses. After a median of 6.8 years of follow-up time, 480 women were diagnosed with breast cancer. We calculated breast cancer rates for women diagnosed with common histologic features and compared breast cancer risk for these women with women with no known breast biopsy experience and a normal mammogram.

Materials and Methods

Data Collection. Benign breast pathology reports were collected and abstracted as part of the New Mexico Mammography Project. The New Mexico Mammography Project is a member of the Breast Cancer Surveillance Consortium, a National Cancer Institute–funded project created to evaluate the effectiveness of mammography screening (22). The benign breast data are linked with the New Mexico Tumor Registry to ascertain the subsequent occurrence of breast cancer. The New Mexico Tumor Registry is a statewide, population-based cancer registry and one of the National Cancer Institute–funded Surveillance, Epidemiology, and End Results registries that provide estimates of cancer incidence, treatment, and survival and mortality rates. The project was reviewed and approved by the University of New Mexico Health Sciences Center Human Research Review Committee.

New Mexico Tumor Registry staff abstracted pathology reports using Systematized Nomenclature of Human and Veterinary Medicine codes. We grouped morphologic terms into broader categories for the analysis. The atypical hyperplasia category includes both lobular and ductal forms. The adenosis category includes adenosis, fibrosing adenosis, and...
Population and Biopsy Selection. Women residing in New Mexico, ages 30 to 89 years, with a benign breast biopsy in our database between 1992 and 2000 were selected for analysis. Women with a known history of breast cancer, mastectomy, or breast implants at the time of biopsy were excluded. Starting with a woman’s first breast biopsy report in the database, we identified any subsequent breast biopsy that occurred within 90 days and repeated the process until the 90 days following the last biopsy were biopsy-free, thus combining the results of all biopsies that occurred over a short period. The purpose of combining biopsy results clustered in time is to capture the most complete diagnosis available. Women diagnosed with ductal carcinoma in situ or invasive breast cancer within 90 days were excluded because we are only interested in following women with an entirely benign diagnosis. Follow-up time begins to accumulate on the 91st day after the diagnosis is complete.

For comparison, we identified women according to the same selection and exclusion criteria with a screening mammogram assigned a “negative” or “benign finding” assessment, with no recommendations for additional evaluation, and with a recommendation to return for routine screening. Women with a known history of breast biopsy, breast cancer, mastectomy, or breast implants at the time of the mammogram were excluded. Women diagnosed with ductal carcinoma in situ or invasive breast cancer within 90 days of the mammogram were excluded. Follow-up time begins to accumulate on the 91st day after the mammogram.

Statistical Analysis. The outcome, breast cancer, was defined as either ductal carcinoma in situ or invasive cancer. Breast cancer rates were calculated for each of the histologic categories described previously. We generated Kaplan-Meier plots (SAS 8.2, LIFETEST procedure) to show the breast cancer accumulation for each histologic group. We used Cox regression (SAS 8.2, PHREG procedure) to generate breast cancer hazard ratios (HR), and the women with negative and benign finding mammograms served as a reference group. Women in the reference group were censored at the time of any subsequent benign biopsies. If a woman initially received a negative mammogram diagnosis and later received a benign biopsy diagnosis, then she is included in both the benign biopsy group and the negative mammogram group, with her follow-up time allocated accordingly.

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We had to consider that a single pathology report often lists multiple histologic features and calculated Pearson correlation coefficients to evaluate the association among histologic diagnoses. Because atypical hyperplasia, cytologic atypia, and lobular carcinoma in situ diagnoses are well documented in the literature in terms of their association with elevated risk, we separated any diagnosis that included one of these high-risk histologies and refer to the remaining as low-risk histologic diagnoses. Existing literature does not provide sufficient guidance for further hierarchical classification among the low-risk histologic diagnoses. Therefore, although the group of women classified as high risk are mutually exclusive of the women in the low-risk groups, we did not use a hierarchical classification scheme for the low-risk diagnoses, and the specific low-risk groups are not mutually exclusive of each other. For example, if a woman has an initial diagnosis, including both adenosis and calcifications, she is included in the rates and HRs for adenosis and for calcifications. However, if her initial diagnosis also includes atypical hyperplasia, she is classified as high risk and only included in the analysis for atypical hyperplasia and not in the analyses of adenosis or calcifications. Each diagnosis group was examined individually; for example, in the analysis of adenosis, women with a low-risk diagnosis that includes adenosis were compared with women with a negative/benign mammogram in a Cox model. The first HR in Table 3 is adjusted for age in deciles. The second HR is further adjusted by including indicator variables for concurrent diagnoses of apocrine metaplasia, calcifications, cysts, fibroadenoma, fibroses, ductal hyperplasia, and inflammation. Analyses of other specific low-risk diagnoses are similarly adjusted for concurrent low-risk diagnoses.

We investigated breast density, approximate menopausal status, and family history of breast cancer as modifiers of the association between benign histologic diagnoses and future
breast cancer development and also adjusted for these factors, age and race/ethnicity, as potential confounders when possible, depending on the availability of data.

Results

Benign breast biopsies were identified for 14,602 women, and screening mammograms with a negative or benign finding assessment were identified for 215,283 women. Eighty-five percent of the pathology reports resulted from surgical biopsies, predominantly excisional and core biopsies, whereas the remaining 15% of the pathology reports were from fine-needle aspirations. Five hundred thirty-two of the 14,602 women with benign breast biopsies received a high-risk diagnosis. Among the women with benign breast biopsies, 93% had only one biopsy to consider, whereas 6.2% had two biopsies in a short period, and 0.4% had three or four biopsies in the diagnostic series. The maximum duration from first to last biopsy in the diagnostic series was 145 days.

Baseline characteristics, including age, race/ethnicity, breast density, and family history of breast cancer in a first-degree relative, are presented in Table 1, stratified into three groups, including women with high-risk histologic diagnoses, women with low-risk histologic diagnoses, and women with screening mammograms assigned a negative or benign finding assessment. The age distributions among the three groups were similar, although women with high-risk histologic diagnoses were slightly older. Although the racial/ethnic distributions were also similar among the three groups, Non-Hispanic White women had a higher representation in the benign biopsy groups compared with the negative mammogram group. Despite considerable missing data for breast density (35-46%), the available data suggest highest breast density among women with high-risk histologic diagnoses followed by women with low-risk histologic diagnoses and the lowest breast density among the negative mammogram group. We also see a slightly higher proportion of women with a family history of breast cancer among women with high-risk histologic diagnoses, although the availability of data was limited (24-35% missing).

The pathology diagnosis was characterized by a single histologic category for 45% of the women, whereas the remaining 55% was characterized by two or more histologic categories. Calcifications exhibited the strongest correlation with other histologic categories, including ductal hyperplasia (0.22), adenosis (0.20), atypical hyperplasia (0.16), and fibrocystic changes (0.16). Fibrocystic changes were positively correlated with ductal hyperplasia (0.15) and calcifications (0.16). Apocrine metaplasia was also correlated with hyperplasia, not otherwise specified (0.15), and ductal hyperplasia was correlated with adenosis (0.14). The strongest negative correlations include fibrocystic changes with fibroadenoma (−0.15),

![Figure 1](https://example.com/figure1.png)

Figure 1. Cumulative incidence of breast cancer following benign breast diagnosis.
fibroses (−0.14), inconclusive (−0.13), negative (−0.21), and other (−0.13). Negative results were also negatively correlated with fibroadenomas (−0.15). The absolute value of the correlation coefficient between all other pairs of histologic categories was ≤0.11 and in most cases <0.06.

Among the 215,283 women with negative mammograms, 6,300 women eventually had a breast biopsy with a benign diagnosis, at which time they were censored and then contributed to the 14,602 women with benign breast biopsies, with their remaining follow-up time allocated accordingly. Among the 14,602 women with benign breast biopsies, 2,021 women eventually had a subsequent breast biopsy with a benign diagnosis; we did not consider these subsequent diagnoses in our analysis. The median observed time at risk following negative mammograms and benign breast biopsies was 2,920 and 2,491 days, respectively.

We identified 480 breast cancer diagnoses among the women with benign breast biopsies and 4,402 breast cancer diagnoses among the women with negative mammograms. The counts of in situ and invasive cancers are listed in Table 2. The breast cancer rates for women who were diagnosed with atypical hyperplasia, cytologic atypia, and lobular carcinoma in situ were 1,148 per 100,000 woman-years, 770 per 100,000 woman-years, and 899 per 100,000 woman-years, respectively. The remaining women with low-risk histologic diagnoses had a breast cancer rate of 466 per 100,000 woman-years, whereas the women who received negative or benign finding assessments for their screening mammograms had a breast cancer rate of 266 per 100,000 woman-years (Table 2). Specific low-risk histologic diagnoses followed by the highest breast cancer rates were adenosis, apocrine metaplasia, calcifications, and hyperplasia. Fibroadenomas and inflammation had the lowest subsequent breast cancer rates.

Figure 1 shows the unadjusted cumulative incidence of breast cancer events among women with high- and low-risk benign breast diagnoses and women with normal mammogram results. Breast cancer incidence following low-risk diagnoses seems steady during the course of the study period and is consistently between the breast cancer incidence experienced by the group of women diagnosed with high-risk diagnoses and the group of women with normal mammograms. There is no sudden increase in cancer incidence following benign diagnosis to suggest that the subsequent risk is due to missed cancer.

Table 3. Breast cancer HRs following benign biopsy

<table>
<thead>
<tr>
<th></th>
<th>HR*</th>
<th>HR* adjusted for other low-risk diagnoses</th>
<th>HR* adjusted for breast density, ethnicity, and family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/benign</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>mammograms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>4.40 (2.73-7.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>3.58 (1.34-9.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>3.20 (1.60-6.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk histologic diagnoses</td>
<td>1.95 (1.77-2.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosis</td>
<td>2.28 (1.64-3.17)</td>
<td>2.72 (1.62-4.56)</td>
<td>2.81 (1.46-5.39)</td>
</tr>
<tr>
<td>Apocrine Metaplasia</td>
<td>3.05 (2.27-4.09)</td>
<td>3.26 (2.05-5.19)</td>
<td>3.89 (2.15-7.04)</td>
</tr>
<tr>
<td>Calcifications</td>
<td>2.27 (1.78-2.89)</td>
<td>2.07 (1.38-3.09)</td>
<td>2.14 (1.12-4.12)</td>
</tr>
<tr>
<td>Cysts</td>
<td>1.64 (1.11-2.43)</td>
<td>1.28 (0.74-2.21)</td>
<td>1.37 (0.71-2.65)</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>1.28 (0.97-1.67)</td>
<td>1.14 (0.82-1.58)</td>
<td>1.01 (0.63-1.63)</td>
</tr>
<tr>
<td>Fibroses</td>
<td>1.94 (1.52-2.46)</td>
<td>1.81 (1.32-2.48)</td>
<td>1.61 (1.05-2.48)</td>
</tr>
<tr>
<td>Hyperplasia, ductal</td>
<td>2.13 (1.70-2.69)</td>
<td>2.18 (1.57-3.02)</td>
<td>1.93 (1.22-3.06)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>1.35 (0.85-2.15)</td>
<td>1.11 (0.56-2.20)</td>
<td>1.71 (0.76-3.81)</td>
</tr>
</tbody>
</table>

*HRs (95% CI) are adjusted for age in deciles.

†HRs adjusted for breast density, ethnicity, and family history of breast cancer are calculated from a subset of women with available data for all of these variables.

‡Women with negative/benign mammograms are the reference group in all models.
The observed breast cancer rates and HRs further contribute to evidence of an increase in breast cancer risk following benign biopsy, including some histologic diagnoses in absence of atypia. Atypical hyperplasia, cytologic atypia, and lobular carcinoma in situ were associated with an elevated breast cancer risk that is consistent with other published data. As a group, the more common low-risk histologic diagnoses and dense breast tissue characterized as fatty or with scattered densities had a HR of 2.09 (95% CI, 1.68-2.60), whereas women with low-risk histologic diagnoses and dense breast tissue had a HR of 3.36 (95% CI, 2.83-3.99).

Discussion

The extent of missing data is noted in Table 1. After limiting the analysis to patients with available data, we adjusted HRs for age, race/ethnicity, breast density, and family history of breast cancer, as well as concurrent diagnoses in specific low-risk categories (Table 3).

We stratified by family history of breast cancer and found that women with low-risk diagnoses and a family history of breast cancer had an age-adjusted HR of 2.33 (95% CI, 1.68-3.22), whereas women with a low-risk diagnosis and no family history of breast cancer had an age-adjusted HR of 2.14 (95% CI, 1.88-2.44). The number of women with a family history of breast cancer is inadequate for further analyses of possible risk modification in the specific low-risk categories.

We stratified according to breast density (Table 4) and found that women with low-risk histologic diagnoses and breast tissue characterized as fatty or with scattered densities had a HR of 2.09 (95% CI, 1.68-2.60), whereas women with low-risk histologic diagnoses and dense breast tissue had a HR of 3.36 (95% CI, 2.83-3.99).

Table 4. Breast cancer HRs following benign biopsy, stratified by approximate menopausal status and breast density

<table>
<thead>
<tr>
<th>HRs* stratified by approximate menopausal status</th>
<th>Fatty/scattered densities</th>
<th>Dense</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age ≤55 y</strong></td>
<td><strong>Age &gt;55 y</strong></td>
<td><strong>Age &gt;55 y</strong></td>
</tr>
<tr>
<td>Negative/benign mammograms</td>
<td>1.00*</td>
<td>1.16 (1.04-1.30)</td>
</tr>
<tr>
<td>Low-risk histologic diagnoses</td>
<td>1.87 (1.64-2.13)</td>
<td>2.39 (2.02-2.83)</td>
</tr>
<tr>
<td>Adenosis</td>
<td>2.51 (1.38-4.57)</td>
<td>3.53 (1.87-6.66)</td>
</tr>
<tr>
<td>Apocrine metaplasia</td>
<td>3.36 (1.93-5.84)</td>
<td>3.68 (2.11-6.42)</td>
</tr>
<tr>
<td>Calcifications</td>
<td>2.16 (1.34-3.50)</td>
<td>2.31 (1.45-3.69)</td>
</tr>
<tr>
<td>Cysts</td>
<td>1.16 (0.59-2.27)</td>
<td>1.70 (0.85-3.39)</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>1.23 (0.86-1.75)</td>
<td>1.08 (0.87-1.37)</td>
</tr>
<tr>
<td>Fibroses</td>
<td>1.52 (0.99-2.33)</td>
<td>2.45 (1.66-3.63)</td>
</tr>
<tr>
<td>Hyperplasia, Ductal</td>
<td>2.13 (1.38-3.29)</td>
<td>2.58 (1.75-3.80)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>1.09 (0.51-2.31)</td>
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</tr>
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</table>

*HRs (95% CI) are adjusted for age in deciles.

†HRs for specific low-risk diagnoses are adjusted for concurrent low-risk diagnoses seen in this list.

‡HRs stratified by breast density are calculated from a subset of women with available breast density scores.

††Women with negative/benign mammograms ages ≤55 y are the reference group in all models stratified by approximate menopausal status.

‡‡Women with negative/benign mammograms with fatty/scattered breast densities are the reference group in all models stratified by breast density.

Figures 2 examines the low-risk histology diagnoses individually over time. We only display curves for groups with larger sample sizes and restrict our interpretation to the first several years, as the curves become erratic due to limited sample size after 4 to 5 years. Women diagnosed with apocrine metaplasia, adenosis, calcifications, ductal hyperplasia, fibroses, and cysts experienced more breast cancer diagnoses than those with normal mammograms. Women diagnosed with inflammation and fibroadenomas did not experience more breast cancer diagnoses than women with normal mammograms.

The age-adjusted HRs and 95% confidence intervals (95% CI) for atypical hyperplasia, cytologic atypia, and lobular carcinoma in situ were 4.40 (2.73-7.09), 3.58 (1.34-9.52), and 3.20 (1.60-6.40), respectively, compared with women with screening mammograms with negative or benign finding assessments (Table 3). The remaining low-risk histologic diagnoses had an age-adjusted HR of 1.95 (95% CI, 1.77-2.15). The term “fibrocystic breast changes” was broadly applied by clinical pathologists, as 44% of the low-risk diagnoses included a similar term (6,128 women with fibrocystic breast changes of the 14,070 women with low-risk diagnoses; Table 2), either alone or in conjunction with other descriptors, with an age-adjusted HR of 2.07 (95% CI, 1.80-2.37). Specific low-risk histologic diagnoses with the strongest associations with subsequent breast cancer development included adenosis, apocrine metaplasia, calcifications, and ductal hyperplasia (Table 3). After adjustment for concurrent low-risk diagnoses, the HRs increased for adenosis, apocrine metaplasia, and ductal hyperplasia, whereas they decreased for other low-risk diagnoses. Cysts were significantly associated with subsequent breast cancer development before adjustment for concurrent diagnoses with HR of 1.64 (95% CI, 1.11-2.43), whereas after adjustment, the HR attenuated and was no longer significant with a HR of 1.28 (95% CI, 0.74-2.21). Fibroadenomas and inflammation diagnoses did not exhibit a notable magnitude of effect or a statistically significant association with subsequent breast cancer development.

When we stratified the data at age 55 years as an approximation for menopausal status, the HRs were consistently higher in the group presumed to be postmenopausal (Table 4). Women with a low-risk histologic diagnosis who were <55 years of age had a HR of 1.87 (95% CI, 1.64-2.13) compared with women 55 years or older with HR of 2.39 (95% CI, 2.02-2.83). Because facility participation with the New Mexico Mammography Project is voluntary and facilities use widely varying data systems and patient forms, missing data for race/ethnicity, breast density, and family history of breast cancer limited our ability to evaluate interactions and confounders. The
slightly modified the association between low-risk histologic diagnosis and breast cancer development in our data, though the extent of missing data limits our ability to evaluate interactions.

The results of these analyses must be considered in the context of several limitations. We did not attempt to distinguish between markers of elevated overall breast cancer risk and lesions with increased risk of local breast cancer occurrence. We did not have complete information about all of the known epidemiologic breast cancer risk factors available for evaluating potential confounders and effect modifiers, as we could not dictate what information was collected by the facilities. The histologic terms were abstracted from clinical pathology reports, meaning each diagnosis was not the result of a consistent team of pathologists working with strictly defined criteria and an algorithm to resolve disagreements, as used in other studies. Furthermore, poor agreement among pathologists about the distinction between low-grade ductal carcinoma in situ and atypical ductal hyperplasia in the absence of a strictly controlled protocol has been discussed elsewhere (29-31). Pathologists also differ in the level of detail they specify on a clinical report, and some may report only the primary histologic feature, whereas others may report multiple features. Whereas some investigators have chosen to compare with the overall population (12), we used women with a normal mammogram as our reference population. Women receiving regular health care, such as mammography or benign breast biopsies, will have a higher chance of cancer diagnosis than those not receiving regular health care. Clearly, the choice of control group could alter the HR estimates.

Physicians who make decisions about patient care and advise patients about the importance of any pathology diagnosis do so based on clinical pathology reports. Although this analysis does not constitute biological evidence of the risk of a particular histologic feature, this analysis is useful as it evaluates the association between actual information provided to practicing physicians and subsequent breast cancer diagnosis.

Acknowledgments

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References

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