

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JULY 21, 2005

VOL. 353 NO. 3

## Benign Breast Disease and the Risk of Breast Cancer

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### ABSTRACT

#### BACKGROUND

Benign breast disease is an important risk factor for breast cancer. We studied a large group of women with benign breast disease to obtain reliable estimates of this risk.

#### METHODS

We identified all women who received a diagnosis of benign breast disease at the Mayo Clinic between 1967 and 1991. Breast-cancer events were obtained from medical records and questionnaires. To estimate relative risks, we compared the number of observed breast cancers with the number expected on the basis of the rates of breast cancer in the Iowa Surveillance, Epidemiology, and End Results registry.

#### RESULTS

We followed 9087 women for a median of 15 years. The histologic findings were nonproliferative lesions in 67 percent of women, proliferative lesions without atypia in 30 percent, and atypical hyperplasia in 4 percent. To date, 707 breast cancers have developed. The relative risk of breast cancer for the cohort was 1.56 (95 percent confidence interval, 1.45 to 1.68), and this increased risk persisted for at least 25 years after biopsy. The relative risk associated with atypia was 4.24 (95 percent confidence interval, 3.26 to 5.41), as compared with a relative risk of 1.88 (95 percent confidence interval, 1.66 to 2.12) for proliferative changes without atypia and of 1.27 (95 percent confidence interval, 1.15 to 1.41) for nonproliferative lesions. The strength of the family history of breast cancer, available for 4808 women, was a risk factor that was independent of histologic findings. No increased risk was found among women with no family history and nonproliferative findings. In the first 10 years after the initial biopsy, an excess of cancers occurred in the same breast, especially in women with atypia.

#### CONCLUSIONS

Risk factors for breast cancer after the diagnosis of benign breast disease include the histologic classification of a benign breast lesion and a family history of breast cancer.

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N Engl J Med 2005;353:229-37.

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**B**ENIGN BREAST DISEASE IS AN IMPORTANT risk factor for a later breast cancer, which can develop in either breast.<sup>1</sup> It encompasses a spectrum of histologic entities, usually subdivided into nonproliferative lesions, proliferative lesions without atypia, and atypical hyperplasias, with an increased risk of breast cancer associated with proliferative or atypical lesions.<sup>2-4</sup> The identification of benign breast disease has become more common as the use of mammography has increased, and thus, having accurate risk estimates for women who receive this diagnosis is imperative.

Important questions remain, however, about the degree of risk associated with the common nonproliferative benign entities and the extent to which family history influences the risk of breast cancer in women with proliferative or atypical lesions. Dupont and Page found that women with nonproliferative disease did not have an increased risk of a later breast cancer.<sup>2</sup> By contrast, a companion study to the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P1) found a relative risk of 1.6 for women who received a diagnosis of a "lower category" of benign breast disease.<sup>5</sup> A limitation of the NSABP study, however, was the lack of central pathological review.

Another major question concerns the possible interplay between atypia and a family history of breast cancer. The Dupont and Page study found that women with atypia and a family history had 11 times the risk of those with nonproliferative lesions and no family history.<sup>2</sup> However, two other major studies of benign breast disease<sup>6,7</sup> did not find a significant interaction between atypia and family history. The duration of increased risk after a finding of benign disease on biopsy is also uncertain.<sup>2,4,8</sup>

Studies of benign breast disease can also clarify whether there is a continuum of breast alterations that culminates in breast cancer. However, it remains unclear which of the benign entities are actual precursors and which reflect a background of increased risk involving all breast tissue in a woman. Determining the extent of agreement between the side (right or left) of the benign lesion and the subsequent breast cancer is one means of assessing these issues.

To investigate these questions, we studied 9087 women with benign breast disease for whom we had follow-up data on breast-cancer events. This cohort has been followed for a median of 15 years, and 707 breast cancers have developed, making this, to our knowledge, one of the largest such studies of its

kind. We report on the risk of breast cancer according to histologic findings, the age at diagnosis of benign breast disease, and the strength of the family history. We also recorded the side of the cancer (ipsilateral or contralateral) and the time to the diagnosis of cancer.

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## METHODS

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### STUDY POPULATION

We accessed data from the Mayo Clinic Surgical Index and Pathology Index to identify all women 18 to 85 years of age who had undergone surgical excision of a benign breast lesion during the 25-year period from January 1, 1967, through December 31, 1991. For women who had more than one biopsy during this period, we used the first sample. The original list contained 12,132 women, but we excluded 1,047 women for any of the following: a diagnosis of breast cancer or lobular carcinoma in situ at, before, or within six months after the biopsy of the benign lesion; mastectomy (unilateral or bilateral) or breast reduction at or before biopsy; or refusal to allow use of their medical records for research.<sup>9</sup> This left 11,085 women. Of these, 1053 (9.5 percent) had no follow-up information after the biopsy. Thus, a total of 10,032 women met our criteria for study entry and had follow-up information. Of these, 945 women had unusable or unavailable biopsy specimens of the benign lesion. The remaining group of 9087 women constitutes our study cohort. The relative risks of breast cancer (described below) did not differ significantly between the 10,032 women who met our criteria and the 9087 women who made up the study cohort (1.59 and 1.56, respectively).

### FAMILY HISTORY AND FOLLOW-UP

A questionnaire designed for this study was used to obtain information about family history and other possible risk factors for breast cancer. Thus, our family-history data were obtained at the time of follow-up contact. We categorized family history as none, weak, or strong. The criteria for a strong family history were as follows: 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 of breast cancer was categorized as weak. The questionnaire also asked about breast-cancer occurrences. Follow-up for breast-cancer events was also obtained through the comprehensive (inpatient and outpatient) Mayo medical

record. Questionnaire information was available for 5619 women (61.8 percent). Of the questionnaires, 604 (10.7 percent) were completed by proxy (the next of kin of a deceased patient). As of August 1, 2004, 7260 (79.9 percent) members of the cohort were still alive. All protocol procedures and patient-contact materials were reviewed and approved by the institutional review board of the Mayo Clinic; returning the contact materials was considered implied consent.

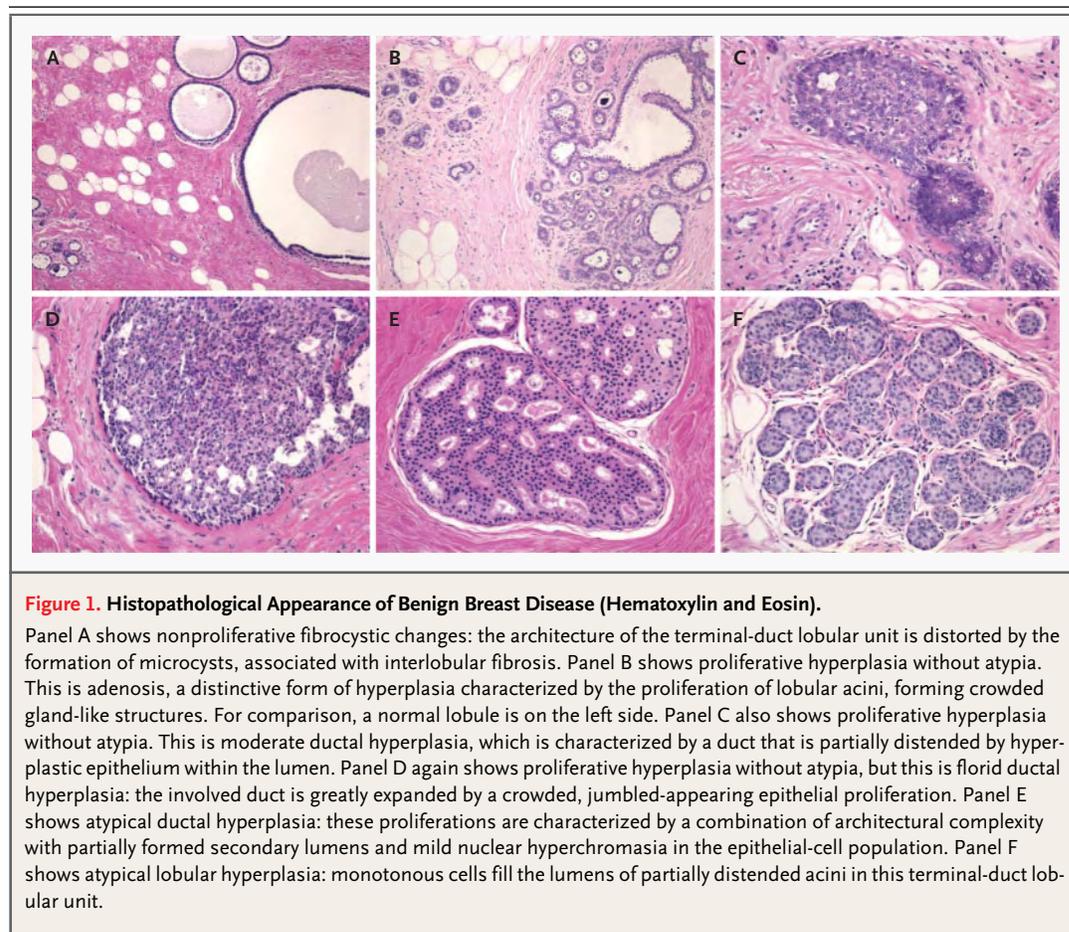
#### HISTOLOGY

Stored hematoxylin-and-eosin-stained sections from each participant were evaluated by a breast pathologist who was unaware of the initial histologic diagnoses and patient outcomes. Biopsy findings were classified according to the criteria of Page et al.<sup>2,10</sup> into the following categories: nonproliferative fibrocystic changes, proliferative fibrocystic changes without atypia, and proliferative fibrocystic changes

with atypia (atypical ductal hyperplasia, atypical lobular hyperplasia, or both) (Fig. 1).<sup>2,10</sup> Biopsy specimens were designated as having proliferative fibrocystic changes if they contained any of the following: ductal hyperplasia (greater than mild), papilloma, radial scar, or sclerosing adenosis. Cysts, fibroadenoma, or columnar changes were considered nonproliferative unless they also contained one of the lesions denoted above.

#### STATISTICAL ANALYSIS

The duration of follow-up was calculated as the number of days from biopsy of the benign lesion to the date of the diagnosis of breast cancer, death, or last contact. We estimated relative risks on the basis of standardized incidence ratios (SIRs), dividing the observed numbers of incident breast cancers by population-based expected counts. We calculated these expected counts by apportioning each woman's follow-up into five-year age and calendar-



period categories, thereby accounting for differences associated with these variables. We used the Iowa Surveillance, Epidemiology, and End Results (SEER) registry as the reference population because of its demographic similarities to the Mayo Clinic population (80 percent of cohort members reside in the upper Midwest). Over 95 percent of our cohort was white, equivalent to that reported in Iowa census data during the study period.<sup>11</sup> In the SIR analyses, we considered the time since the original biopsy as a time-dependent variable and all other factors as fixed.

Associations between the risk of breast cancer and histologic findings, the age at diagnosis of be-

nign breast disease, and the strength of the family history of cancer, as well as pairwise combinations of these variables, were examined with the use of Cox proportional-hazards regression analysis. The main effects for each categorized variable and the corresponding interaction terms were included in each model, and the statistical significance of each interaction was evaluated with the use of a multiple-degree-of-freedom likelihood-ratio test.

We studied ipsilateral and contralateral breast cancer as a function of the time since biopsy by estimating the relative risk of cancer in the same as compared with the opposite breast for five-year intervals. When calculating the incidence of ipsilat-

**Table 1. Characteristics of the Women According to the Histologic Category of Benign Breast Disease.\***

Characteristic	All Women (N=9087)	Nonproliferative Disease (N=6061)	Proliferative Disease without Atypia (N=2690)	Atypical Hyperplasia (N=336)
Percentage of total	100.0	66.7	29.6	3.7
Age at biopsy — no. of women (%)				
<40 yr	1841 (20.3)	1500 (24.7)	323 (12.0)	18 (5.4)
40–49 yr	2474 (27.2)	1621 (26.7)	770 (28.6)	83 (24.7)
50–59 yr	2145 (23.6)	1297 (21.4)	759 (28.2)	89 (26.5)
60–69 yr	1639 (18.0)	1034 (17.1)	522 (19.4)	83 (24.7)
≥70 yr	988 (10.9)	609 (10.0)	316 (11.7)	63 (18.8)
Mean age at biopsy — yr	51.4±14.3	49.9±14.8	53.9±12.6	57.8±12.3
Menopausal status at biopsy — no. of women (%)†				
Premenopausal (<45 yr)	2948 (32.4)	2246 (37.1)	652 (24.2)	50 (14.9)
Perimenopausal (45–55 yr)	2583 (28.4)	1610 (26.6)	871 (32.4)	102 (30.4)
Postmenopausal (>55 yr)	3556 (39.1)	2205 (36.4)	1167 (43.4)	184 (54.8)
Family history of breast cancer — no. of women (%)				
Unknown	4279 (47.1)	2970 (49.0)	1170 (43.5)	139 (41.4)
Known	4808 (52.9)	3091 (51.0)	1520 (56.5)	197 (58.6)
None	2668 (55.5)	1735 (56.1)	831 (54.7)	102 (51.8)
Weak	1174 (24.4)	756 (24.5)	378 (24.9)	40 (20.3)
Strong	966 (20.1)	600 (19.4)	311 (20.5)	55 (27.9)
Breast-cancer status as of August 2004 — no. of women (%)				
Negative	8380 (92.2)	5682 (93.7)	2426 (90.2)	272 (81.0)
Positive	707 (7.8)	379 (6.3)	264 (9.8)	64 (19.0)
Vital status — no. of women (%)				
Deceased	1827 (20.1)	1172 (19.3)	566 (21.0)	89 (26.5)
Alive	7260 (79.9)	4889 (80.7)	2124 (79.0)	247 (73.5)

\* Plus-minus values are means ±SD.

† Menopausal status was categorized according to the age at breast biopsy.

eral cancer, we censored follow-up on women with contralateral cancer after the date of diagnosis. Similarly, when calculating the incidence of contralateral cancer, we censored follow-up on women with ipsilateral cancer after the date of diagnosis. Data on women missing information on the side of the cancer or women who had bilateral biopsies or cancer were not included in these analyses. This approach yields identical numbers of person-years for each type of event. As a result, the length of follow-up is no longer a factor in the analysis and the relative risks are equivalent to simple ratios of event counts. We therefore used properties of the binomial distribution to obtain exact P values and 95 percent confidence intervals for these relative risks.<sup>12</sup> Statistical tests were two-sided, and analyses were conducted with the use of SAS (SAS) and Splus (Insightful) software.

## RESULTS

## CHARACTERISTICS OF PATIENTS AND PATHOLOGICAL SPECIMENS

The final cohort consisted of 9087 women with benign breast disease as determined by open surgical biopsy. Table 1 shows the age at the time of the biopsy, likely menopausal status on the basis of age, and the strength of the family history of breast cancer according to the histologic findings for the benign lesion. The broad histologic classifications included nonproliferative disease in 6061 (66.7 percent), proliferative disease without atypia in 2690 (29.6 percent), and atypical hyperplasia in 336 (3.7 percent). Figure 1 shows examples of these lesions. The mean age was 51.4 years, but women with nonproliferative findings were slightly younger, whereas those with atypia tended to be older (mean age,

**Table 2. Risk Factors for Breast Cancer after the Diagnosis of Benign Breast Disease.\***

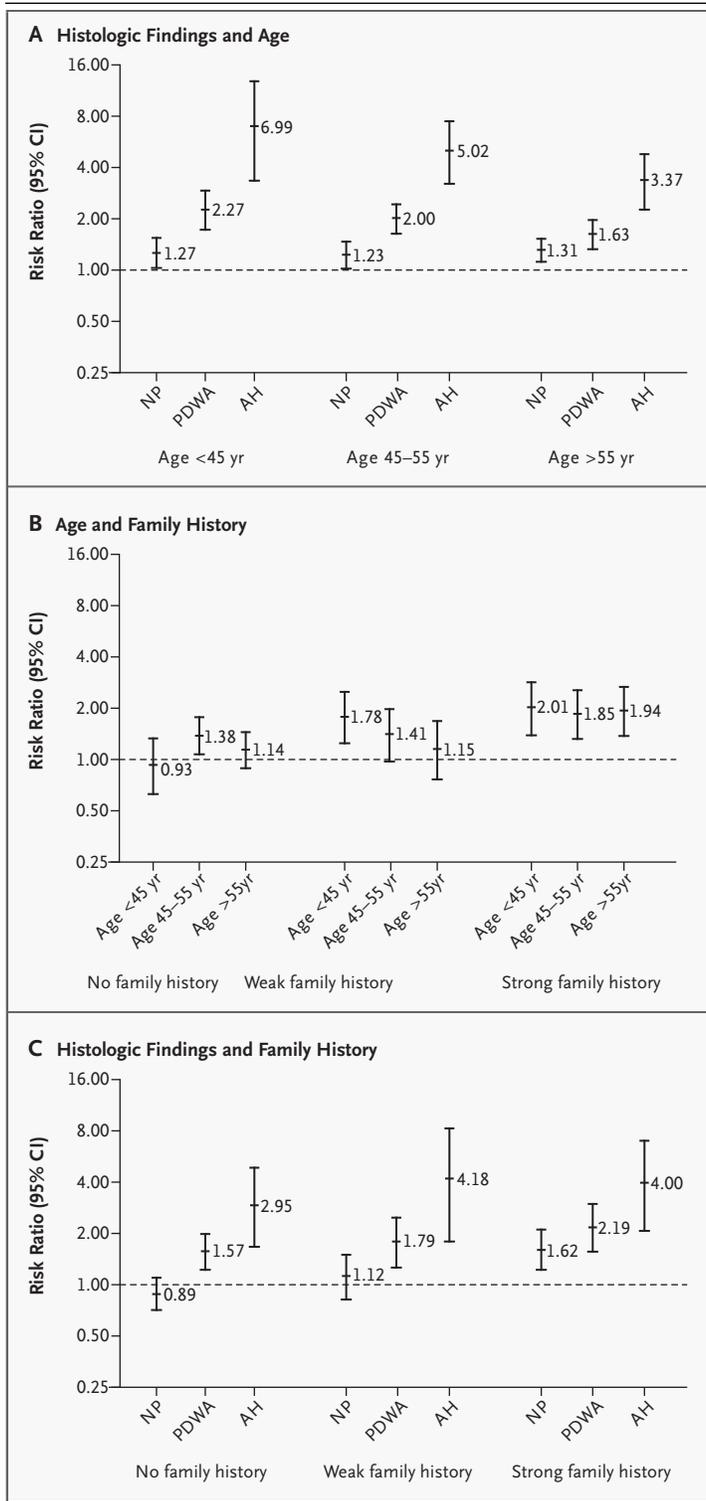
Characteristic	No. of Women	Person-Years	No. of Observed Events	No. of Expected Events	Relative Risk (95% CI)†
Overall	9087	144,881	707	453.0	1.56 (1.45–1.68)
Age at diagnosis of benign breast disease					
<30 yr	726	13,593	21	11.5	1.83 (1.13–2.80)
30–39 yr	1115	20,169	71	38.3	1.85 (1.45–2.34)
40–49 yr	2474	45,780	212	136.3	1.56 (1.35–1.78)
50–59 yr	2145	34,100	196	125.9	1.56 (1.35–1.79)
60–69 yr	1639	21,364	142	94.5	1.50 (1.27–1.77)
≥70 yr	988	9,874	65	46.6	1.40 (1.08–1.78)
Menopausal status‡					
Premenopausal (age <45 yr)	2948	54,419	169	106.1	1.59 (1.36–1.85)
Perimenopausal (age 45–55 yr)	2583	45,872	245	153.4	1.60 (1.40–1.81)
Postmenopausal (age >55 yr)	3556	44,590	293	193.6	1.51 (1.35–1.70)
Histologic findings					
Nonproliferative disease	6061	99,109	379	297.7	1.27 (1.15–1.41)
Proliferative disease without atypia	2690	41,610	264	140.2	1.88 (1.66–2.12)
Atypical hyperplasia	336	4,161	64	15.1	4.24 (3.26–5.41)
Family history of breast cancer§					
None	2668	44,974	171	145.4	1.18 (1.01–1.37)
Weak	1174	21,472	94	65.9	1.43 (1.15–1.75)
Strong	966	18,087	110	57.0	1.93 (1.58–2.32)

\* Numbers of women, person-years, and events may not sum to overall totals because of rounding.

† The relative risk reflects the observed number of events as compared with the number expected on the basis of Iowa SEER data. All analyses account for the effects of age and calendar period. CI denotes confidence interval.

‡ Menopausal status was categorized according to the age at breast biopsy.

§ Information on family history was available for 4808 of the 9087 women.



**Figure 2. Risk-Factor Interaction Profiles for Benign Breast Disease, Comparing the Number of Events Observed with the Number Expected.**

Expected events account for age and calendar period and are calculated with the use of Iowa SEER rates. CI denotes confidence interval, NP nonproliferative disease, PDWA proliferative disease without atypia, and AH atypical hyperplasia.

weakly positive in 1174 (24.4 percent), and strongly positive in 966 (20.1 percent). More women with atypia than without atypia had a strong family history of breast cancer (27.9 percent vs. 19.8 percent,  $P=0.06$ ). The risk of cancer was highest in the group with atypia: breast cancer developed in 64 of the 336 women (19.0 percent).

**FEATURES OF BENIGN BREAST DISEASE AND SUBSEQUENT RISK OF BREAST CANCER**

Patients in the cohort were followed for a median of 15 years. A total of 1827 women (20.1 percent) had died and 7260 (79.9 percent) were alive as of August 2004. We have documented 707 breast cancers to date. The median time from the original biopsy to the diagnosis of breast cancer was 10.7 years. Table 2 shows the estimated relative risks of breast cancer associated with the age at the initial biopsy, the strength of the family history, menopausal status, and histologic findings of the biopsy, as compared with expected population-based incidence. The estimated relative risk of breast cancer in the cohort was 1.56 (95 percent confidence interval, 1.45 to 1.68). The risk was inversely associated with the age at biopsy, with younger women having a greater risk than older women. The type of benign breast disease identified at biopsy was a major predictor of risk. Atypical hyperplasia had a relative risk of 4.24 (95 percent confidence interval, 3.26 to 5.41), proliferative disease without atypia had a relative risk of 1.88 (95 percent confidence interval, 1.66 to 2.12), and nonproliferative lesions had a relative risk of 1.27 (95 percent confidence interval, 1.15 to 1.41). Family history was an independent risk factor. For women with no known family history of breast cancer, the relative risk was only 1.18 (95 percent confidence interval, 1.01 to 1.37), as compared with 1.43 (95 percent confidence interval, 1.15 to 1.75) for women with a weak family history and 1.93 (95 percent confidence interval, 1.58 to 2.32) for those with a strong family history.

49.9 and 57.8 years, respectively;  $P<0.001$ ). Information on family history was available for 4808 women and was negative in 2668 (55.5 percent),

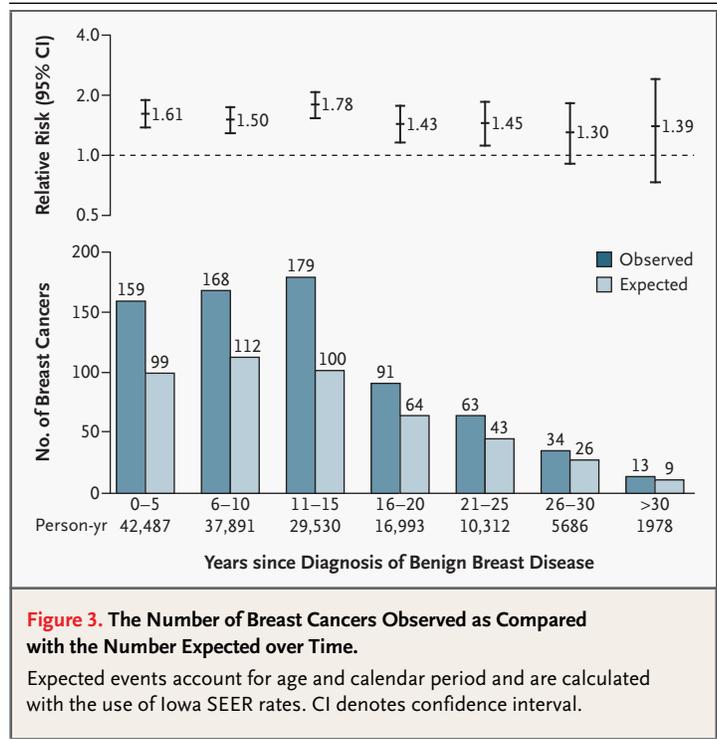
Figure 2 shows possible interactions between pairs of the major risk factors of age, histologic findings, and family history. No significant interactions were observed between age and family history or between histologic findings and family history, including atypia and family history. However, there was a significant interaction between age and histologic findings ( $P=0.05$ ): the risk of breast cancer was 6.99 times the expected risk among women who received a diagnosis of atypia before the age of 45 years; the risk was 5.02 times the expected risk when the atypia was diagnosed between the ages of 45 and 55 years and 3.37 times the expected risk when it was diagnosed after the age of 55 years. An important finding was that for women with non-proliferative disease and no family history or a weak family history, there was no increase in the risk of breast cancer.

**TIME COURSE AND SIDE OF BREAST CANCER AFTER BENIGN BREAST DISEASE**

Figure 3 shows the observed and expected numbers of cancers at five-year intervals. The excess risk persisted for at least 25 years after the initial biopsy and perhaps for 30 years or more, but accuracy was low after 25 years. Figure 4 shows a further breakdown of breast cancers into ipsilateral or contralateral according to the histologic findings in the benign lesion. Of the 616 unilateral cancers, 342 (55.5 percent) developed in the same breast as the initial biopsy and 274 (44.5 percent) developed in the contralateral breast. In the remaining 91 cases, there were bilateral events, either benign or malignant, or information on the side of the cancer was missing. During the first 10 years, there was an excess of ipsilateral cancers, with relative risks of ipsilateral as compared with contralateral cancer of 1.88 (95 percent confidence interval, 1.33 to 2.64) for years 0 through 5 and 1.34 (95 percent confidence interval, 0.96 to 1.85) for years 6 through 10. The 35 women with atypia in whom breast cancer developed within 10 years after the initial biopsy were 2.5 times as likely ( $P=0.02$ ) to have the cancer in the same breast as in the opposite breast.

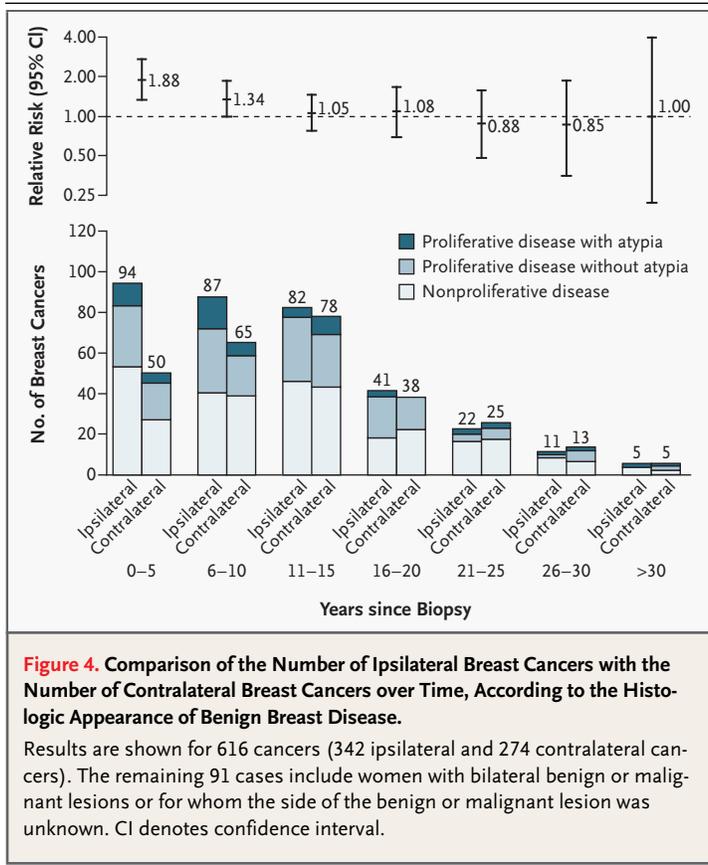
**DISCUSSION**

Retrospective and prospective studies have shown a relative risk of breast cancer of 1.5 to 1.6 for women with benign breast disease as compared with women in the general population.<sup>2,5-7,13-21</sup> The histologic appearance of the benign lesion is a major



determinant of risk, yet not all large studies have had access to tissue for re-review. Our investigation was based on a single-institution resource with long-term and complete follow-up for cancer events. All samples containing the benign lesion were read by a breast pathologist who applied current histologic classifications. More than 700 breast cancers developed in this cohort, giving our study good statistical power. The relative risk of breast cancer for our cohort overall was 1.56 (95 percent confidence interval, 1.45 to 1.68), and this increased risk persisted for at least 25 years after the initial biopsy.

The histologic appearance of the benign lesion is strongly associated with the risk of breast cancer. For biopsies with nonproliferative findings, the relative risk was 1.27 (95 percent confidence interval, 1.15 to 1.41), as compared with a relative risk of 1.88 (95 percent confidence interval, 1.66 to 2.12) for findings of proliferative changes but no atypia and of 4.24 (95 percent confidence interval, 3.26 to 5.41) for a finding of atypical hyperplasia. When the family history is known, risk profiles can be refined. For women with nonproliferative findings and no family history or a weak family history of breast cancer, we observed no increased risk. This finding is important, because a sizable proportion



of women with benign breast disease are in this group (52 percent of our cohort with a known family-history status). Dupont and Page made a similar observation in their 1985 report.<sup>2</sup> However, a recent NSABP study found a significantly increased risk of breast cancer among women with lower-category benign breast disease, including nonproliferative disease.<sup>5</sup> In the NSABP P1 trial, which included more than 13,000 women, 1376 had a breast biopsy with benign findings over a mean follow-up period of 79 months. Breast cancer developed in 47 of these women. On the basis of pathology reports from contributing centers, the investigators reported a relative risk of 1.6 among women with lower category findings on breast biopsy as compared with P1 participants who did not undergo a breast biopsy.<sup>5</sup>

In our study, the degree of family history was an independent risk factor. In women with a strong family history of breast cancer, even nonproliferative findings were associated with a risk ratio of 1.62. This subgroup may parallel the high-risk NSABP cohort.<sup>5</sup> Women with atypia are at significantly in-

creased risk, but a family history did not significantly modify the atypia-associated risk (Fig. 2). The risk was four times the expected risk among women with atypia and a family history of breast cancer, regardless of the degree of their family history; among women with atypia without a family history of breast cancer, the risk ratio was 2.95 (95 percent confidence interval, 1.65 to 4.87).

The age at the diagnosis of benign breast disease appears to modify the risks related to the histologic appearance of benign breast disease. The presence of atypia in women under 45 years of age conveyed twice the risk observed among women over 55 years of age (6.99 and 3.37, respectively), which might relate, in part, to menopausal status. The Breast Cancer Detection and Demonstration Project showed that the risk of breast cancer among premenopausal women with atypia was elevated by a factor of 12.0 (95 percent confidence interval, 2.0 to 68.0), as compared with 3.3 among postmenopausal women with atypia (95 percent confidence interval, 1.1 to 10.0), but the numbers of patients in the study were small.<sup>22</sup> The Nurses Health Study also showed an increased risk of breast cancer among premenopausal women with atypia.<sup>7</sup> However, in the NSABP study of women with lower categories of benign breast disease, the risk of breast cancer was greatest among postmenopausal women.<sup>5</sup>

Understanding the risk associated with benign breast disease is important because the increasing use of mammography has increased the frequency of breast biopsies, most of which yield benign findings. In a retrospective study of women undergoing annual mammographic screening, Elmore et al. found that 18.6 percent of women underwent a biopsy after 10 screening mammograms.<sup>23</sup> The use of hormone therapy may also affect the frequency of breast biopsies. Chlebowski et al., reporting for the Women's Health Initiative investigators, found that relatively short-term therapy with estrogen plus progestin increased the percentage of women with abnormal mammograms, a major indicator for breast biopsy.<sup>24</sup>

Regarding the possibility of malignant precursors within benign breast disease, we have information on the side and the time to breast cancer for 616 unilateral events. An excess of breast cancers occurred in the same breast during the first years of follow-up, especially in women with atypia (Fig. 4). This finding suggests that precursors to breast cancer exist in benign breast disease. Work in model systems of early steps in mammary carcinogenesis

has identified alterations in key regulatory indicators that can be studied in selected benign breast lesions.<sup>25,26</sup>

In summary, our study shows that histologic features, the age at biopsy, and the degree of family history are major determinants of the risk of breast cancer after the diagnosis of benign breast disease. We found no increased risk among women with nonproliferative lesions, unless a strong family history was present. No significant interaction between atypia and family history was apparent. The excess

risk of cancer in the ipsilateral breast in the first 10 years after the diagnosis of benign breast disease, especially in women with atypia, points to the presence of precursors in some women.

Supported by a Department of Defense Center of Excellence Grant (FEDDAMD17-02-1-0473-1), a grant (R01 CA46332) from the National Institutes of Health, a grant (BCTR99-3152) from the Susan G. Komen Breast Cancer Foundation, the Breast Cancer Research Foundation, and the Andersen Foundation.

We are indebted to Joel Worra and Dr. Piet de Groen for database development; to Teresa Allers, Mary Amundsen, Mary Campion, Lois Penheiter, and Romayne Thompson for data collection; and to Ann Harris and the Survey Research Center for patient follow-up.

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