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Complex Fibroadenoma and Breast Cancer Risk: A Mayo Clinic Benign Breast Disease Cohort Study^a

Dr. Aziza Nassar, MD, Dr. Daniel W. Visscher, MD, Dr. Amy C. Degnim, MD, Messr. Ryan D. Frank, Messr. Robert A. Vierkant, Dr. Marlene Frost, PhD, Dr. Derek C. Radisky, PhD, Dr. Celine M. Vachon, PhD, Ms Ruth A. Kraft, Dr. Lynn C. Hartmann, MD, and Dr. Karthik Ghosh, MD

Department of Laboratory Medicine and Pathology (Dr Nassar) and Department of Cancer Biology (Dr Radisky), Mayo Clinic, Jacksonville, Florida, and Division of Anatomic Pathology (Dr Visscher), Department of Surgery (Dr Degnim), Division of Biomedical Statistics and Informatics (Messr Frank and Vierkant), Division of Oncology Research (Dr Frost), Division of Epidemiology (Dr Vachon), Division of Nephrology and Hypertension (Ms Kraft), Division of Medical Oncology (Dr Hartmann), and Division of General Internal Medicine (Dr Ghosh), Mayo Clinic, Rochester, Minnesota

Abstract

Purpose—To examine the breast cancer risk overall among women with simple fibroadenoma or complex fibroadenoma and to examine the association of complex fibroadenoma with breast cancer through stratification of other breast cancer risks.

Methods—The study included women aged 18 to 85 years from the Mayo Clinic Benign Breast Disease Cohort who underwent excisional breast biopsy from 1967 through 1991. Within this cohort, women who had fibroadenoma were compared to women who did not have fibroadenoma. Breast cancer risk (observed vs expected) across fibroadenoma levels was assessed through standardized incidence ratios (SIRs) by using age- and calendar-stratified incidence rates from the Iowa Surveillance, Epidemiology, and End Results registry. Analyses were performed overall, within subgroups of involution status, with other demographic characteristics (age, year of biopsy, indication for biopsy, and family history), and with histologic characteristics, including overall impression (nonproliferative disease, proliferative disease without atypia [PDWA], or atypical hyperplasia).

Results—Fibroadenoma was identified in 2,136 women (noncomplex, 1,835 [85.9%]; complex, 301 [14.1%]). SIR for noncomplex fibroadenoma was 1.49 (95% CI, 1.26–1.74); for complex fibroadenoma, it was 2.27 (95% CI, 1.63–3.10) (test for heterogeneity in SIR, $P=.02$). However,

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Reprints: Aziza Nassar, MD, Department of Laboratory Medicine and Pathology, 4500 San Pablo Rd, Jacksonville, FL 32224 (nassar.aziza@mayo.edu).

Conflict of Interest

The authors declare that they have no conflicts of interest.

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women with complex fibroadenoma were more likely to have other, concomitant high-risk histologic characteristics (eg, incomplete involution and PDWA). In analyses stratified by involution status and PDWA, complex fibroadenoma was not an independent risk marker for breast cancer.

Conclusions—Complex fibroadenoma does not confer increased breast cancer risk beyond other established histologic characteristics.

Keywords

benign breast disease; breast cancer; cancer risk; fibroadenoma; Mayo Clinic Benign Breast Disease Cohort

Introduction

Fibroadenoma (FA) is a benign breast lesion that occurs most commonly in premenopausal women, but it can occur in women at any age [1]. Several reports have described a higher risk of subsequent breast carcinoma among patients who have FA, with relative risks (RRs) ranging from 1.48 to 1.7 [1–5]. At the tissue level, FA is a benign tumor composed of both epithelial and stromal components. *Complex FAs* are FAs with associated histologic characteristics, including cysts (≥ 3 mm), sclerosing adenosis, epithelial calcifications, or papillary apocrine metaplasia [2]. A prior report from Dupont et al [2] showed that the RR of invasive breast cancer (BC) was 2.17 times higher for patients with FA than for matched controls (95% CI, 1.5–3.2). The RR increased to 3.10 for women with complex FAs (95% CI, 1.9–5.1) and remained elevated for more than 20 years after diagnosis [2]. Further increases in risk were reported for patients with FA who had 1) benign proliferative disease without atypia (PDWA) in the surrounding parenchyma adjacent to the FA (RR, 3.47; 95% CI, 1.8–6.8), 2) atypical hyperplasia in the surrounding parenchyma (RR, 7.29; 95% CI, 2.2–24), and 3) a family history of BC (RR, 3.72; 95% CI, 1.4–10).

Currently, FA is diagnosed when a patient presents with a palpable lump or has a breast imaging procedure that shows an abnormality that is investigated with percutaneous biopsy. Because FA is a benign finding, most patients with FA are subsequently followed by their primary care providers. Hence, the risk association of FA with BC, and by type of FA (complex or simple), should be clarified so that women with FA can be appropriately counseled about future screening and risk reduction strategies.

In the present study, we investigated the BC risk associated with FA, both overall and stratified into complex and simple FA. In addition, we evaluated the associations stratified by individual histologic criteria (ie, cysts ≥ 3 mm, sclerosing adenosis, epithelial calcifications, and papillary apocrine metaplasia) to clarify whether a specific feature of complex FA was more closely associated with risk. Lastly, we evaluated the effect of proliferative disease and atypical hyperplasia (within FA or adjacent to FA, or both) to further stratify risk.

Methods

Study Population

The study was conducted with the Mayo Clinic Benign Breast Disease (BBD) Cohort [6,7]. The characteristics of the patients, the inclusion and exclusion criteria, and the assessment of the pathologic specimens have been described extensively in earlier reports [6,7]. Briefly, the study population consisted of 9,076 women aged 18 to 85 years who underwent surgical excision of a benign breast lesion at Mayo Clinic in Rochester, Minnesota, from January 1, 1967, through December 31, 1991. Details about family history of BC and subsequent BC events were obtained from medical records and questionnaires sent to patients and next of kin. Family history of BC was classified as *negative* (if there was no family history of BC); *strong* (if there was 1 first-degree relative with BC before age 50 years or 2 relatives with BC, with 1 being a first-degree relative); or *weak* (for any family history not classified as strong).

Histologic Examination

If the woman had more than 1 biopsy during the study period, we used findings from the earliest biopsy performed. For each participant, stored hematoxylin-eosin–stained sections were evaluated by an experienced breast pathologist (D.W.V.). The biopsy findings were classified according to the criteria proposed by Page and Anderson [8] as nonproliferative disease, PDWA, or atypical hyperplasia (AH) (including atypical ductal hyperplasia or atypical lobular hyperplasia, or both). PDWA criteria were ductal hyperplasia (more than mild), papillomas, radial scar, or sclerosing adenosis (2 foci of lobular units involved and 1 focus with a diameter larger than that of a normal lobule). Other histologic features, such as cysts, apocrine metaplasia, FA, sclerosing adenosis (<2 lobular units involved), or columnar cell changes, were considered to be nonproliferative unless they also contained 1 of the described proliferative lesions. Sufficient tissue was available to assess the presence or absence of FA for the 9,076 women. FA was diagnosed when a fibroepithelial lesion with both ductal epithelial and stromal fibrous proliferations measured at least 4.0 mm in diameter [9]. Another breast pathologist (A.N.) carried out a second review of all cases with FA and categorized the parenchyma as either PDWA or AH.

At secondary review, all FAs were classified as *complex* or *noncomplex*. According to previously published criteria [8], FA was classified as complex (Figure) when it contained 1 or more of the following: cyst diameter 3 mm or larger, sclerosing adenosis, epithelial calcifications, and papillary apocrine metaplasia. In addition, other coexisting histologic findings were recorded for each biopsy sample: nonproliferative and proliferative lesions (as described above), and AH. Each sample was evaluated for the presence of surrounding breast parenchyma adjacent to the FA and was defined as sufficient for evaluation if it was at least 0.5 cm² in area or if it had 5 lobular units (a lobular unit is a cluster of acini that drain into a terminal duct lobular unit). Finally, the location of all PDWA and AH findings was documented (as within the FA, in adjacent parenchyma, or in both locations).

The adjacent breast parenchymal tissue was also evaluated for extent of lobular involution. Lobular involution was classified as *no involution* (0% involuted lobules), *partial involution* (1%-74% involuted lobules), or *complete involution* (≥75% involuted lobules) [7].

The Mayo Clinic Institutional Review Board approved the research. Informed consent was also received from all participants.

Statistical Analysis

Data were summarized descriptively as frequencies and percentages for categorical variables and as means and ranges for continuous variables. We used χ^2 tests of significance to compare the presence of FA across the levels of categorical variables (including age at biopsy, era of biopsy, indication for biopsy, histologic impression, extent of lobular involution, and family history of BC).

Duration of follow-up was calculated as the number of days after biopsy of a benign lesion to the date of BC diagnosis, death, or last contact. In addition, if women had prophylactic mastectomies or a diagnosis of lobular carcinoma in situ, their data were censored at the date of such an occurrence. Standardized incidence ratios (SIRs) with 95% CIs were used to estimate RRs; SIRs were calculated by dividing the actual number of women who had BC by the number expected to have BC. The expected number was determined by dividing the patient's follow-up into 5-year periods according to the patient's age and according to the calendar period; this accounted for differences related to the variables. The reference population was the Iowa Surveillance, Epidemiology, and End Results registry [6]. Like the Mayo Clinic patients, 80% of the reference population lived in the Upper Midwest, and the 2 groups were similar demographically (eg, >95% of both groups were white) [6]. SIRs were calculated for the overall group and for subgroups defined by histologic impression and other BBD characteristics. Potential heterogeneity in SIRs across subgroups was assessed with Poisson regression analysis; the offset term was the log-transformed expected event rate for each patient. All statistical analyses were 2-sided and used SAS statistical software (SAS Institute Inc). *P* values less than .05 were considered statistically significant.

Results

Clinicopathologic Characteristics

A total of 9,076 women comprised the cohort: 6,940 (76.5%) with no FA; 1,835 (20.2%) with simple FA; and 301 (3.3%) with complex FA. Mean age was 52.2 years for women without FA, 45.8 years for women with simple FA, and 50.2 years for women with complex FA. Nearly half the women with simple FA were younger than 45 years, compared with 40% for women with complex FA (Table 1).

Simple FA was detected more often as a lump (57.2%) compared to complex FA (49.0%). Complex FA was more common in the postmammographic era between 1982 and 1991 (65.8%) compared to the premammographic era before 1982 (34.2%). The proportion of women with FA who also had AH was low overall but approximately 4 times greater in the complex FA group (6.0%) than in the simple FA group (1.6%).

Involution differed among women according to FA status, with a general trend toward less complete involution in women with FA compared to those without. Complete involution was seen less frequently in women with simple FA (n=216; 15.1%) and complex FA (n=27; 11.7%) than in women without FA (n=1,588; 23.3%) ($P=.002$). Family history of BC was not common among women with either simple FA or complex FA. Strong family history was noted for only small percentages of women with simple FA (8.7%) or complex FA (11.7%).

Association of FA and Other Risk Factors With BC Risk

BC occurred in 151 (8.2%) of the 1,835 women with simple FA and in 40 (13.3%) of the 301 women with complex FA (Table 2). The RR of BC for the entire FA cohort was 1.60 (95% CI, 1.38–1.85), which was similar to the RR for the group without FA (RR, 1.51; 95% CI, 1.40–1.63) and for the group with simple FA (RR, 1.49; 95% CI, 1.26–1.74). However, the group with complex FA had a slightly increased RR of 2.27 (95% CI, 1.63–3.10) compared with the general population (test for heterogeneity in RR between simple FA and complex FA, $P=.02$).

For women with simple FA, the risk of BC did not differ substantively across subcategories of age, era of biopsy, involution status, and family history of BC (Table 2). However, women with simple FA presenting with a breast lump (RR, 1.95; 95% CI, 1.59–2.38) had a higher risk than those with FA detected on mammography (RR, 1.09; 95% CI, 0.80–1.44; $P<.001$).

As expected, there was a significant difference in risk when simple FA was associated with proliferative disease compared to nonproliferative disease (RR, 1.20; 95% CI, 0.97–1.45), PDWA (RR, 2.73; 95% CI, 1.99–3.66), or AH (RR, 4.07; 95% CI, 1.49–8.86; $P<.001$) (Table 2). Similar trends were seen for women with complex FA, but results were not statistically significant, in part because the sample sizes were smaller (test for heterogeneity in RR between simple FA and complex FA: $P=.35$ for NP, $P=.32$ for PDWA, and $P=.59$ for AH). For women with proliferative disease, the location of proliferative histologic findings in association with FA was also studied (Table 3). The BC risk was not different when the PDWA was located adjacent to the FA or within the FA ($P=.97$). Similarly, the risk was not influenced by the location of AH, whether adjacent to or within the FA ($P=.41$). Findings were similar when we looked at simple and complex FA separately, although the numbers in each category were too small in the subgroup analysis.

Of the 4 proliferative disease components of FA, sclerosing adenosis was predominant (79.4%; 239 of 301). No individual component conferred an increased risk of BC compared to the others (Table 4), although these analyses were limited by power and should be interpreted with caution. The presence of any 1 of the histologic criteria was not associated with increased risk of BC, but when 2 (RR, 2.67; 95% CI, 1.52–4.33) or more (RR, 7.77; 95% CI, 3.13–15.99) histologic features of complex FA were found simultaneously in the complex FA, there was an increase in BC risk. However, the group of women with 3 lesions in a complex FA was very small (6.3%; 19 of 301) (Table 4).

Discussion

In this study, the overall risk of BC for women with FA was slightly elevated (RR, 1.60; 95% CI, 1.38–1.85) and similar to the risk of women without FA (RR, 1.51; 95% CI, 1.40–1.63). Women with complex FA had a slightly higher RR of 2.27 (95% CI, 1.63–3.10) than those with simple FA (RR, 1.49; 95% CI, 1.26–1.74; test for heterogeneity in RR, 0.022). However, in analyses stratified by histologic impression, these differences attenuated greatly, suggesting that the risk of BC with FA was associated with the greatest degree of epithelial proliferation (PDWA or AH, whether within or adjacent to the FA) rather than with the mere presence of FA.

Dupont et al [2] described BC risk in women with FAs almost 2 decades ago. In a retrospective cohort study of 1,835 women with FA biopsied from 1950 through 1968, BC developed in 87 (4.7%). In a comparison with 2 control groups, 1 of which included the patient's sister-in-law, Dupont et al concluded that FA confers an overall RR of 2.17 (95% CI, 1.5–3.2). However, this risk increased to 3.10 (95% CI, 1.9–5.1) for 422 women with complex FA, including 29 (6.9%) who had BC. Dupont et al [2] further showed that this increased risk persisted for decades after the initial diagnosis. In the present study, 2,136 women with FAs were studied and BC developed in 191 women (8.9%) during a 20-year follow-up. The BC risk was slightly elevated for women with FA and more so for women with complex FA. Similar to the study findings of Dupont et al, although women with complex FA were at slightly elevated BC risk, the risk was not significantly different between women with simple FA and women with no FA (Table 2). It is notable that these 2 cohorts are among the largest cohorts of women with FA studied to date.

In the present study, among women with FA, the presence of PDWA or AH was associated with greater BC risk compared to nonproliferative disease ($P<.001$) (Table 2). PDWA (including usual ductal hyperplasia other than mild, sclerosing adenosis, papillomas, and radial scar) was noted in 22.9% (490 of 2,136) of all women with FA and more frequently in women with complex FA (218 of 301; 72.4%). In comparison, Dupont et al [2] reported an incidence of 13.7% for PDWA with FA and an increased BC risk of 3.9 for FA with PDWA. In contrast, AH was seen with 2.2% of all FA but was relatively more common with complex FA (6.0%) than with simple FA (1.6%). The frequency of atypical ductal hyperplasia (1.2%) was somewhat lower in the study by Kuijper et al [1] than in the study by Dupont et al [2] (1.7%). In the present study, the elevated risk for women with FA was not significantly different from that for women without FA (RR, 1.51; 95% CI, 1.40–1.63). These findings suggest that the elevated risk for women with FA is similar to the overall BBD cohort risk rather than specific for the presence of the FA.

The study by Dupont et al [2] reported risk association according to the location of the proliferative disease—within the FA or outside the FA. In our study, PDWA was associated with a slightly increased risk irrespective of whether it was present within the FA or outside the FA. The presence of AH within the FA was associated with an elevated risk, but the number of patients was small (RR, 6.03; 95% CI, 2.21–13.12). Hence, our study suggests that the location of the PDWA or AH within the FA or outside the FA did not influence BC risk (Table 3). Once again, these data suggest that the risk of BC in women with FA is

driven mostly by the histologic features present in association with the FA, such as PDWA or AH.

In studying the association with other known risk factors for BC, we noted that the association of involution and risk in women with FA (RR, 1.72; 95% CI, 1.27–2.28 for no involution and RR, 0.80; 95% CI, 0.41–1.40 for complete involution; $P=.03$) was similar to the association for women with BBD overall [6]. Although there was no significant association between family history of BC and BC risk for women with FA ($P=.08$), women with a strong family history of BC had higher risk than those with no family history. In summary, the BC risk for the 3 categories of BBD in this cohort of women with FA was similar to the risk of women with BBD overall, suggesting that the elevated risk in this population was likely reflecting the underlying risk associated with BBD rather than with the FA itself.

Dupont et al [2] reported elevated BC risk for women with complex FA. When we assessed the 4 histologic components of FA for associations with BC risk in the present study, none of the components of complex FA (cysts >3 mm, sclerosing adenosis, epithelial calcifications, or papillary apocrine changes) was significantly associated with BC risk (Table 4). However, the presence of 2 or more of these components increased the risk of BC compared to only 1 factor ($P=.007$). BC risk was noted to be slightly higher for women with complex FA and PDWA as well as for those with complex FA and AH, but the difference was not significant ($P=.17$) (Table 2). This is likely because complex FA includes the histologic findings of PDWA, such as sclerosing adenosis, and the reported increased risk with complex FA reflects the risk associated with PDWA. As confirmed by a prior study from our group, sclerosing adenosis was found to be an independent risk marker for BC (SIR for BC, 2.10) [10].

All 2,136 FAs in the present study were excised, and none had concurrent BC. Prior reports showed the co-occurrence of in situ and invasive cancer ranging from 0.2% to 2% [1,11–13], and Kuijper et al [1] reported carcinoma in situ (both ductal carcinoma in situ and lobular carcinoma in situ) in 2.0% of patients with FA. As a result, several authors have opted for conservative management of FA in younger women [1]. Another study showed that a large proportion of FAs in women younger than 20 years resolves spontaneously [14]. Studies have also reported that carcinoma in situ arising within FA is found mostly in women older than 35 years; therefore, removal of FAs in this age group has been suggested [1]. Although the present report did not specifically compare conservative management with excision of FA, the finding that malignancy within FA is rare suggests that a conservative approach with observation of FA is reasonable unless the mass increases in size over time.

Ciatto et al [15] noted that the SIR for histologically confirmed FAs was slightly increased (SIR, 2.0; 95% CI, 1.4–2.7), whereas there was no apparent risk of nonexcised, clinically or mammographically detected FAs (SIR, 0.97; 95% CI, 0.7–1.4). Those investigators suggested that BC risk assessment may be biased, specifically when the analysis is limited to surgically excised FAs. All patients in the present study had surgical excision of their FAs, and we found a mild increase in BC risk for women with complex FA who presented with a lump compared with FA detected by mammogram, although the difference was not

statistically significant (Table 2). The reason for this is unclear. However, surgical excision by itself should not alter risk for FA since the lesion by itself is considered a nonproliferative histologic entity that is not associated with an increase in BC risk (RR for NP disease, 1.21; 95% CI, 1.08–1.34) (Table 2).

The strength of the present study is its large BBD cohort exceeding 9,000 women, including more than 2,100 women with FA and women who were found to have FA in both the premammographic era and the postmammographic era. Samples were reviewed extensively by 2 experienced breast pathologists who used established criteria previously reported. The limitation of the current study is that all women had a surgical biopsy performed, and thus we cannot comment on the current practice of clinical and radiologic observation alone, which is advised for mammographically detected small lesions found in some women.

Conclusion

The risk of BC for women with FA of the breast is similar to that for women with a diagnosis of BBD. Complex FA does not confer increased risk of BC beyond that of other established histologic features such as PDWA and AH. Therefore, the management of complex FA should be based on the associated histologic findings of BBD, such as PDWA or AH.

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Abbreviations

AH	atypical hyperplasia
BBD	benign breast disease
BC	breast cancer
FA	fibroadenoma
PDWA	proliferative disease without atypia
RR	relative risk
SIR	standardized incidence ratio

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Figure.
Complex fibroadenoma with sclerosing adenosis (crowded glands in a fibrotic stroma)
(hematoxylin-eosin; original magnification $\times 10$).

Table 1
Clinicopathologic Characteristics of the Entire Cohort by FA Status

Characteristic	Status, No. (%) ^a			P Value ^b
	No FA (n=6,940)	Simple FA (n=1,835)	Complex FA (n=301)	
Age at BBD diagnosis, y				.007
<45	1,973 (28.4)	888 (48.4)	118 (39.2)	
45–55	2,109 (30.4)	390 (21.3)	68 (22.6)	
>55	2,858 (41.2)	557 (30.4)	115 (38.2)	
Era of biopsy				.03
Premammographic	3,490 (50.3)	752 (41.0)	103 (34.2)	
Postmammographic	3,450 (49.7)	1,083 (59.0)	198 (65.8)	
Indication for biopsy				.01
Missing data	388	156	15	
Lump	4,007 of 6,552 (61.2)	960 of 1,679 (57.2)	140 of 286 (49.0)	
Mammogram	2,545 of 6,552 (38.8)	719 of 1,679 (42.8)	146 of 286 (51.0)	
Overall histologic impression				<.001
NP disease	4,439 (64.0)	1,534 (83.6)	65 (21.6)	
PDWA	2,215 (31.9)	272 (14.8)	218 (72.4)	
AH	286 (4.1)	29 (1.6)	18 (6.0)	
Involution				.002
Missing data ^c	138	401	71	
None	1,019 of 6,802 (15.0)	506 of 1,434 (35.3)	60 of 230 (26.1)	
Partial	4,195 of 6,802 (61.7)	712 of 1,434 (49.7)	143 of 230 (62.2)	
Complete	1,588 of 6,802 (23.3)	216 of 1,434 (15.1)	27 of 230 (11.7)	
Family history of breast cancer				.20
Missing data	30	11	1	
None	4,618 of 6,910 (66.8)	1,181 of 1,824 (64.7)	194 of 300 (64.7)	
Weak	1,610 of 6,910 (23.3)	484 of 1,824 (26.5)	71 of 300 (23.7)	
Strong	682 of 6,910 (9.9)	159 of 1,824 (8.7)	35 of 300 (11.7)	

Abbreviations: AH, atypical hyperplasia; BBD, benign breast disease; FA, fibroadenoma; NP, nonproliferative; PDWA, proliferative disease without atypia.

^aNumbers may not add up to the total number of patients because of missing values for some variables.

^b χ^2 test comparing distributions of characteristics across simple FA vs complex FA.

^cNo normal terminal duct lobular units were present on the slide, so involution could not be assessed.

Table 2

Relative Risk of Breast Cancer by FA Status and Other Characteristics

Characteristic	No FA				Simple FA				Complex FA				All FA			
	Total No.	Obs Cases, No.	Exp Cases, No.	SIR ^a (95% CI)	Total No.	Obs Cases, No.	Exp Cases, No.	SIR ^a (95% CI)	Total No.	Obs Cases, No.	Exp Cases, No.	SIR ^a (95% CI)	Total No.	Obs Cases, No.	Exp Cases, No.	SIR ^a (95% CI)
Overall	6,940	683	454.76	1.50 (1.39–1.62)	1,835	151	101.55	1.49 (1.26–1.74)	301	40	17.58	2.27 (1.63–3.10)	2,136	191	119.13	1.60 (1.38–1.85)
Age at BBD diagnosis, y																
<45	1,973	150	104.85	1.43 (1.21–1.68)	888	60	38.28	1.57 (1.20–2.02)	118	16	5.08	3.15 (1.80–5.11)	1,006	76	43.36	1.75 (1.38–2.19)
45–55	2,109	251	163.20	1.54 (1.35–1.74)	390	48	27.66	1.74 (1.28–2.30)	68	12	4.52	2.65 (1.37–4.63)	458	60	32.18	1.86 (1.42–2.40)
>55	2,858	282	186.71	1.51 (1.34–1.70)	557	43	35.61	1.21 (0.87–1.63)	115	12	7.98	1.50 (0.78–2.63)	672	55	43.59	1.26 (0.95–1.64)
<i>P</i> value ^b				.78				.20				.12				.07
Era of biopsy																
Prenammnographic	3,490	412	242.99	1.70 (1.54–1.87)	752	75	44.32	1.69 (1.33–2.12)	103	17	6.57	2.59 (1.51–4.14)	855	92	50.89	1.81 (1.46–2.22)
Postnammnographic	3,450	271	211.77	1.28 (1.13–1.44)	1,083	76	57.23	1.33 (1.05–1.66)	198	23	11.01	2.09 (1.32–3.14)	1,281	99	68.24	1.45 (1.18–1.77)
<i>P</i> value ^b				.003				.14				.51				.13
Indication for biopsy																
Lump	4,007	422	267.07	1.58 (1.43–1.74)	960	100	51.18	1.95 (1.59–2.38)	140	23	7.66	3.00 (1.90–4.51)	1,100	123	58.84	2.09 (1.74–2.49)
Mammogram	2,545	242	163.02	1.48 (1.30–1.68)	719	47	43.26	1.09 (0.80–1.44)	146	17	9.3	1.83 (1.06–2.93)	865	64	52.56	1.22 (0.94–1.55)
<i>P</i> value ^b				.44				<.001				.12				<.001
Overall histologic impression																
NP disease	4,439	347	289.92	1.20 (1.07–1.33)	1,534	100	83.62	1.20 (0.97–1.45)	65	6	3.32	1.81 (0.66–3.93)	1,599	106	86.93	1.22 (1.00–1.47)
PDWA	2,215	262	148.59	1.76 (1.56–1.99)	272	45	16.46	2.73 (1.99–3.66)	218	29	13.38	2.17 (1.45–3.11)	490	74	29.84	2.48 (1.95–3.11)
AH	286	74	16.25	4.55 (3.58–5.72)	29	6	1.47	4.07 (1.49–8.86)	18	5	0.89	5.65 (1.84–13.16)	47	11	2.36	4.67 (2.33–8.35)
<i>P</i> value ^b				<.001				<.001				.17				<.001
Involution																
None	1,019	126	65.44	1.93 (1.60–2.29)	506	38	25.01	1.52 (1.08–2.09)	60	10	2.9	3.45 (1.65–6.35)	566	48	27.9	1.72 (1.27–2.28)
Partial	4,195	425	279.56	1.52 (1.38–1.67)	712	66	43.14	1.53 (1.18–1.95)	143	18	9.33	1.93 (1.14–3.05)	855	84	52.47	1.60 (1.28–1.98)
Complete	1,588	110	101.86	1.08 (0.89–1.30)	216	10	13.27	0.75 (0.36–1.39)	27	2	1.68	1.19 (0.14–4.28)	243	12	14.95	0.80 (0.41–1.40)
<i>P</i> value ^b				<.001				.06				.22				.03
Family history of breast cancer																

Characteristic	No FA				Simple FA				Complex FA				All FA			
	Total No.	Obs Cases, No.	Exp Cases, No.	SIR ^a (95% CI)	Total No.	Obs Cases, No.	Exp Cases, No.	SIR ^a (95% CI)	Total No.	Obs Cases, No.	Exp Cases, No.	SIR ^a (95% CI)	Total No.	Obs Cases, No.	Exp Cases, No.	SIR ^a (95% CI)
None	4,618	375	292.36	1.28 (1.16–1.42)	1,181	84	61.54	1.36 (1.09–1.69)	194	20	10.93	1.83 (1.12–2.83)	1,375	104	72.47	1.44 (1.17–1.74)
Weak	1,610	205	110.57	1.85 (1.61–2.13)	484	46	29.02	1.59 (1.16–2.11)	71	12	4.2	2.86 (1.48–4.99)	555	58	33.22	1.75 (1.33–2.26)
Strong	682	101	50.61	2.00 (1.63–2.42)	159	21	10.4	2.02 (1.25–3.09)	35	8	2.29	3.49 (1.51–6.87)	194	29	12.7	2.28 (1.53–3.28)
<i>P</i> value ^b				<.001				.27				.24				.08

Abbreviations: AH, atypical hyperplasia; BBD, benign breast disease; Exp, expected; FA, fibroadenoma; NP, nonproliferative; Obs, observed; PDWA, proliferative disease without atypia; SIR, standardized incidence ratio.

^aThe standardized incidence ratio compares the observed number of breast cancer events with the number expected on the basis of Iowa Surveillance, Epidemiology, and End Results data. All analyses account for the effects of age and calendar period.

^bTest for heterogeneity in risk of breast cancer across levels of attribute.

Table 3

Risk of Breast Cancer According to Location of Proliferative Histologic Findings Within the FA or Outside the FA

Characteristic	All FA			
	Total No.	Obs Cases, No.	Exp Cases, No.	SIR ^a (95% CI)
PDWA in relation to FA				
Outside the FA	295	45	18.08	2.49 (1.81–3.33)
Within the FA	195	29	11.75	2.47 (1.65–3.54)
<i>P</i> value ^b				.97
AH in relation to FA				
Outside the FA	28	5	1.36	3.67 (1.19–8.54)
Within the FA	19	6	0.99	6.03 (2.21–13.12)
<i>P</i> value ^b				.41

Abbreviations: AH, atypical hyperplasia; Exp, expected; FA, fibroadenoma; Obs, observed; PDWA, proliferative disease without atypia; SIR, standardized incidence ratio.

^aThe standardized incidence ratio compares the observed number of breast cancer events with the number expected on the basis of Iowa Surveillance, Epidemiology, and End Results data. All analyses account for the effects of age and calendar period.

^bTest for heterogeneity in risk of breast cancer was only between outside the FA and within the FA.

Table 4
Association of Individual Complex FA Criteria With Risk of Breast Cancer Among Women With a Complex FA

Characteristic	Women, No.	Person-years, No.	Observed Events, No.	Expected Events, No.	SIR ^a (95% CI)	P Value ^b
Cysts >3 mm						.10
No	211	3,976	24	12.53	1.92 (1.23–2.85)	
Yes	90	1,573	16	4.85	3.30 (1.89–5.36)	
Sclerosing adenosis						.09
No	62	1,138	4	3.42	1.17 (0.32–2.99)	
Yes	239	4,412	36	13.95	2.58 (1.81–3.57)	
Epithelial calcifications						.35
No	270	4,995	37	15.29	2.42 (1.70–3.34)	
Yes	31	554	3	2.08	1.44 (0.30–4.20)	
Papillary apocrine metaplasia						.07
No	221	4,060	25	13.09	1.91 (1.24–2.82)	
Yes	80	1,490	15	4.29	3.50 (1.96–5.77)	
Complex FA lesions, No.						.007
1	181	3,385	17	10.48	1.62 (0.94–2.60)	
2	101	1,850	16	6.00	2.67 (1.52–4.33)	
3	19	315	7	0.90	7.77 (3.13–15.99)	

Abbreviations: FA, fibroadenoma; SIR, standardized incidence ratio.

^aThe standardized incidence ratio compares the observed number of breast cancer events with the number expected on the basis of Iowa Surveillance, Epidemiology, and End Results data. All analyses account for the effects of age and calendar period.

^bTest for heterogeneity in risk of breast cancer across levels of attribute.