Published in final edited form as:
Cancer Causes Control. 2010 June ; 21(6): 821–828. doi:10.1007/s10552-010-9508-7.

A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer

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Abstract

Objective—We used a nested case–control design within a large, multi-center cohort of women who underwent a biopsy for benign breast disease (BBD) to assess the association of broad histologic groupings and specific histologic entities with risk of breast cancer.

Methods—Cases were all women who had a biopsy for BBD and who subsequently developed breast cancer; controls were individually matched to cases and were women with a biopsy for BBD who did not develop breast cancer in the same follow-up interval as that for the cases. After exclusions, 1,239 records (615 cases and 624 controls) were available for analysis. We used conditional logistic regression to estimate odds ratios and 95% confidence intervals (CIs).

Results—Relative to non-proliferative BBD/normal pathology, the multivariable-adjusted odds ratio for proliferative lesions without atypia was 1.45 (95% CI 1.10–1.90), and that for atypical hyperplasia was 5.27 (95% CI 2.29–12.15). The presence of multiple foci of columnar cell

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hyperplasia and of complex fibroadenoma without atypia was associated with a non-significantly increased risk of breast cancer, whereas sclerosing adenosis, radial scar, and papilloma showed no association with risk.

Conclusion—Our results indicate that, compared to women with normal pathology/non-proliferative disease, women with proliferative disease without atypia have a modestly increased risk of breast cancer, whereas women with atypical hyperplasia have a substantially increased risk.

Keywords

Benign breast disease; Proliferative disease; Atypical hyperplasia; Breast cancer

Introduction

Benign breast disease (BBD) encompasses a wide variety of histologic entities, which have been broadly classified into non-proliferative lesions, proliferative lesions without atypia, and hyperplasia with atypia [1,2]. With the increased use of mammography, more benign lesions are being detected, and accurately estimating the risk of breast cancer for specific histologic categories is of great importance to guide clinical management. Previous studies have shown that, relative to non-proliferative BBD, women with proliferative lesions without atypia are at slightly increased risk of subsequent breast cancer, whereas women with proliferative lesions with atypia have a substantially higher risk [3–9]. However, it is less clear whether histologic entities such as complex fibroadenoma, sclerosing adenosis, radial scar, and papilloma are associated with increased risk in the absence of atypical hyperplasia [4,9–20]. In addition, the role of modifying factors, such as age at diagnosis of BBD, menopausal status, family history of breast cancer in a first-degree relative, and time since BBD diagnosis on risk of breast cancer, remains to be clarified.

We used a nested case–control design within a large, multi-center cohort of women with biopsy-confirmed BBD to assess the association of specific histologic groupings and entities with risk of subsequent breast cancer.

Methods and materials

The study was conducted within a cohort of 20,697 women who underwent a biopsy for BBD in three centers (Toronto, Canada; Portland, OR, USA; and London, UK). The three cohorts are described in Table 1. The study protocol was approved by the institutional review boards at all four sites (Toronto, London, Portland, and the New York coordinating center).

Histologic review

At each center, slides were reviewed by a designated pathologist, and histologic sections were classified according to the criteria developed by Page and Anderson [21] and the subsequent consensus conference of the College of American Pathologists [22] without knowledge of the case–control status of the study subjects. In addition, pathologists from Portland and London, but not Toronto, had a joint session to standardize criteria.

Although many histologic entities are included in the rubric BBD, the relevant lesions with respect to the risk of subsequent breast cancer are those which are of epithelial origin. These lesions include fibroadenoma, sclerosing adenosis, radial scar, solitary papilloma, and hyperplasia with or without atypia [22–24]. Ductal epithelial hyperplasias display a spectrum of changes ranging from mild to florid. They are classified further as proliferative disease without atypia or atypical ductal hyperplasia, depending on the architectural patterns, and the cytologic appearance of the cells.

For our primary analyses, diagnoses of BBD were grouped into three categories based on the most advanced lesion: normal pathology or non-proliferative lesions (cysts, fibrosis, apocrine metaplasia, simple fibroadenoma); proliferative disease without atypia (mild, moderate, or florid epithelial hyperplasia; columnar cell hyperplasia; complex fibroadenoma; sclerosing adenosis; radial scar; papilloma); and atypical hyperplasia (ductal, lobular, columnar cell with atypia, and fibroadenoma with atypia). Table 2 gives the frequency of specific BBD histologic entities and their classification into three broad risk categories. In addition to these broad histologic categories, we assessed the association of individual histologic entities which may influence subsequent risk of breast cancer independent of associated proliferative disease. These included complex fibroadenoma without atypia, sclerosing adenosis, radial scar, papilloma, and columnar cell hyperplasia [24]. Where the numbers permitted, we distinguished between focal and multiple lesions, because the latter are more likely to be associated with increased risk [9].

Case and control definition

Cases were women who had a biopsy for BBD with a subsequent diagnosis of in situ or invasive breast cancer. In each cohort, controls were women with a biopsy for BBD who were alive but had not developed breast cancer during the same follow-up period as that for the corresponding cases. In the London and Portland cohorts, controls were individually matched to cases (1:1) on age and on age at diagnosis of BBD (with additional matching in the Portland cohort on the duration of membership in Kaiser Permanente health plan). In the Toronto cohort, five controls had been randomly selected for each case from non-case subjects using risk-set sampling for an earlier study [25], but for this study, one control was randomly sampled from the available controls. In each cohort, controls were selected with replacement, and were eligible to be selected again or to become cases subsequently. For this reason, although 1,325 women were selected from the three cohorts, there were a total of 1,362 records in the analysis, 665 case records and 697 control records (Table 3). After exclusions, 1,239 records with a biopsy for BBD (615 breast cancer cases and 624 controls) were available for analysis, and a total of 1,145 women were available for the matched set analysis (559 matched pairs and nine case–control sets with one case and two controls) (Table 3).

Statistical analysis

We used conditional logistic regression to estimate odds ratios and 95% confidence intervals (CIs) for the association between the different histologic groupings and specific types of BBD and risk of subsequent breast cancer. Models with only the matching variables as well as fully adjusted models including breast cancer risk factors were fitted. Breast cancer risk factors included age at menarche (<12, 12, 13, 14–19, or missing); age at first birth (continuous); number of pregnancies (continuous); menopausal status (premenopausal, perimenopausal, postmenopausal); and family history of breast cancer in a first-degree relative (no, yes, or missing). We also examined whether risk varied according to whether the subsequent breast cancer was ipsilateral or contralateral to the index BBD lesion. In further analyses, we tested for interactions between histology and potential effect modifiers, including age (<50 vs. ≥50), menopausal status (premenopausal versus postmenopausal), family history of breast cancer in a first-degree relative (no versus yes), duration of follow-up (< 15 vs. ≥15 years), and center (London, Toronto, Portland), by referring 2* the absolute difference in the log likelihoods of the model with and without the interaction terms to the χ^2 distribution with degrees of freedom equal to the number of interaction parameters. We conducted a number of sensitivity analyses. First, we excluded the cases of in situ breast cancer ($n = 17$) from the analysis. Second, in order to account for the possibility that women diagnosed shortly following baseline might have had a preexisting breast cancer, we excluded cases diagnosed during the first year and the first 3 years of follow-up. Third, we repeated the main analysis by center. Finally, in order to use all

1,239 women, we repeated the main analysis using unconditional logistic regression. All analyses were performed in SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the study subjects are summarized in Table 4. Thirty-six percent of women had normal pathology ($n = 73$) or non-proliferative disease ($n = 367$); 60.9% had proliferative disease without atypia; and 3.6% had proliferative disease with atypia. At the time of BBD biopsy, most women were between 40 and 49 years old and most were premenopausal. Fifteen percent of women had a family history of breast cancer in a first-degree relative. Mean age at biopsy increased with severity of the lesion, as did the prevalence of a family history of breast cancer in a first-degree relative, particularly in the group with atypia (29.5%).

Over a mean of 15.4 years of follow-up of the cohort, 615 breast cancer cases were ascertained. The mean age at diagnosis of breast cancer was 58.4 years. Risk of breast cancer increased with increasing severity of the lesion. Relative to normal pathology/non-proliferative BBD, the multivariable-adjusted odds ratio for proliferative lesions without atypia was 1.45 (95% CI 1.10–1.90), and that for atypical hyperplasia was 5.27 (95% CI 2.29–12.15) (Table 5). Women with atypical ductal hyperplasia and atypical lobular hyperplasia appeared to be at increased risk of breast cancer; however, the estimates were extremely imprecise due to small numbers.

Women with multiple columnar lesions and women with complex fibroadenoma without atypia had a non-significantly increased risk, whereas sclerosing adenosis, radial scar, and papilloma were not associated with risk (Table 5).

Information on laterality of the BBD lesion was available for 1,233 records (99.5%); information on laterality of subsequent breast cancer was available for 408 of the 615 breast cancer case records (66.1%). Of these, 198 women had breast cancer in the ipsilateral breast; 198 women had breast cancer in the contralateral breast; and 12 women had bilateral breast cancer. Among women with proliferative disease without atypia the odds ratio for ipsilateral breast cancer was 1.47 (95% CI 0.93–2.34), and among women with atypical hyperplasia the odds ratio for ipsilateral breast cancer was 8.17 (95% CI 1.51–44.32). The corresponding odds ratios for contralateral breast cancer were 1.43 (95% CI 0.89–2.32) and 5.98 (95% CI 1.88–19.06).

Exclusion of cases of in situ carcinoma of the breast had no effect on the risk estimates. When cases of breast cancer diagnosed during the first year ($n = 6$) and first 3 years of follow-up ($n = 89$) were excluded, the estimates for the effect of proliferative lesions without atypia and for proliferative lesions with atypia were not materially different from those shown in Table 3 (first year: OR 1.48, 95% CI 1.13–1.95 and 5.29, 95% CI 2.30–12.20, respectively; first 3 years: OR 1.44, 95% CI 1.08–1.93 and 4.82, 95% CI 2.06–11.26, respectively). The associations with breast cancer risk of epithelial proliferation without atypia and atypical hyperplasia did not differ by center ($p = 0.4$) (data not shown).

Unconditional logistic regression using all 1,239 women confirmed the results of the conditional logistic regression, although the magnitude of the estimates was somewhat smaller. The multivariable-adjusted odds ratios for proliferative lesions without atypia and for proliferative lesions with atypia were 1.68 (95% CI 1.33–2.13) and 3.49 (95% CI 1.74–7.02), respectively.

In stratified analyses, the association of atypical hyperplasia with breast cancer risk was stronger in younger versus older women and premenopausal versus postmenopausal women. The association of proliferative disease without atypia with breast cancer differed little by age but appeared stronger in postmenopausal women (Table 6). The interaction of histologic

category with age was not statistically significant, whereas the interaction of histologic category with menopausal status was statistically significant ($p < 0.01$). Due to the small number of women with both atypical hyperplasia and a positive family history of breast cancer, we combined proliferative lesions with and without atypia in order to assess heterogeneity by family history of breast cancer. In women with no family history the OR for breast cancer given any proliferative disease was 2.00 (95% CI 1.42–2.80), whereas in women with a family history it was 1.05 (95% CI 0.69–1.61), but the interaction was not statistically significant ($p = 0.20$). The OR for breast cancer given a shorter duration of follow-up (<15 years) was twofold higher than that for longer duration of follow-up (≥15 years), and the interaction between length of follow-up and histology was statistically significant ($p = < 0.01$).

Discussion

This study, the largest cohort study of BBD to date, indicates that women with proliferative breast lesions without atypia have a slightly increased risk of breast cancer, whereas women with atypical hyperplasia have a substantially increased risk. When atypical hyperplasia was examined by histologic subgroup, both atypical ductal and atypical lobular hyperplasia were associated with increased risk, although the estimates of association were imprecise. Our estimates of the risk of breast cancer among women with proliferative lesions without atypia and with proliferative lesions with atypia relative to women with nonproliferative lesions are similar to those of other large cohort studies of BBD [3,5–9].

We found no clear association between side of the BBD lesion and side of the subsequent breast cancer. Among women with proliferative disease without atypia and atypical hyperplasia, odds ratios for subsequent breast cancer in the ipsilateral breast were somewhat higher than among those for breast cancer in the contralateral breast, but the CIs were wide and overlapping. Our findings concerning laterality should to be interpreted cautiously because information on laterality of the breast cancer was missing on one-third of cases. Furthermore, the numbers of ipsilateral and contralateral breast cancers among women with atypical hyperplasia were small ($n = 15$ for both ipsilateral and contralateral). Previous cohort studies have also found higher risk of breast cancer in the ipsilateral breast, particularly among women with atypical hyperplasia [8,26,27].

Studies that have assessed the risk associated with of specific histologic entities within the broad category of proliferative disease without atypia, including fibroadenoma [4,9,11–13, 16], sclerosing adenosis [16,18], radial scar [14–17], and papilloma [10,16,19], have given conflicting results. Some of these discrepancies may be due to the use of different referent groups (non-proliferative disease versus general population), difference in how advanced the lesions were, small numbers of breast cancer cases with specific lesions, and small effect sizes associated with these lesions. Thus, it is unclear whether these specific entities increase the risk of breast cancer independent of their association with proliferative disease without atypia. In this study, the presence of multiple columnar lesions and complex fibroadenoma without atypia were associated with a non-significantly increased risk of breast cancer, whereas sclerosing adenosis, radial scar, and papilloma showed no association with risk.

Some studies have indicated that the risk associated with atypical lobular hyperplasia is greater than that associated with atypical ductal hyperplasia [7,16], whereas others have found no difference in risk [9,28]. Although our point estimate for atypical lobular hyperplasia was higher than that for atypical ductal hyperplasia, there was considerable overlap between the CIs for the two estimates.

Our finding that the association of atypical hyperplasia with breast cancer was stronger among younger women and premenopausal women compared to older women and postmenopausal

women, respectively, agrees with the results of several other studies [1,6–8]. A modifying effect of age or menopausal status on risk among women with proliferative disease without atypia is less clear. We found no difference in risk among younger and older women with proliferative disease without atypia, whereas Hartmann et al. [8] reported a somewhat higher risk among women <45 years of age compared to women >55 years of age. Other studies [5, 6,8] have found that the risk of breast cancer did not differ in premenopausal and postmenopausal women with proliferative disease without atypia, and Ashbeck et al. [13] noted a tendency toward higher risk among presumed postmenopausal women (≥55 years) compared to presumed premenopausal women (<55 years).

Proliferative disease without atypia and atypical hyperplasia were more strongly associated with risk for follow-up of <15 years compared to follow-up of ≥15 years, and the interaction was statistically significant ($p = < 0.01$). In women followed for ≥15 years the ORs for both proliferative disease without atypia and proliferative disease with atypia were elevated but not statistically significant. Our finding is in agreement with those from several studies which suggest that the risk of breast cancer decreases with increasing length of follow-up [10,27, 29]; however, other studies have observed no clear decrease [5,7,8,22,26,28].

Several issues affecting studies of the association of specific BBD features with risk of breast cancer deserve comment. First, some studies which examined the risk of breast cancer among women with biopsy-diagnosed BBD have used non-proliferative disease as the referent group [3,5–7,9,17]. However, several studies which have used the general population or women who have not undergone biopsy as the reference group suggest that women with non-proliferative disease may be at slightly increased risk of breast cancer [4,8,12,28]. Thus, our risk estimates based on including non-proliferative lesions in the reference group may be underestimates of the true risk (expressed relative to that for women with no breast pathology). Second, the classification of specific lesions may differ between different diagnostic centers and pathologists [30,31]. We tried to counteract this by having all pathologists use the same classification scheme; in addition, pathologists from Portland and London, but not Toronto, had a joint session to standardize criteria. For this reason, we carried out a sensitivity analysis excluding Toronto from the analysis, and the results were unchanged. In addition, the consistency of our results with those from studies which have included centralized pathology review is striking. Furthermore, the study results did not differ by study center ($p = 0.4$).

A number of limitations of this study should be mentioned. Due to the small numbers, the risk estimates for ductal, lobular, and columnar atypical hyperplasia were imprecise, a limitation common to most previous studies. Small numbers of atypical hyperplasia also restricted our ability to examine it in combination with other histologic features, such as sclerosing adenosis, radial scar, and papillomas. In addition, small numbers precluded assessment of the interaction between family history and proliferative disease with atypia. We lacked information on features, such as calcifications, which some studies [3,13,22] have found to be associated with increased risk. Finally, information on some breast cancer risk factors was either not available (breastfeeding) or was missing for some women (body mass index, hormone therapy).

In conclusion, this large cohort study of BBD demonstrated that, compared to women with normal pathology or non-proliferative disease, women with proliferative disease without atypia have a modestly increased risk of breast cancer, whereas women with atypical hyperplasia have a substantially increased risk. Our results also suggest that menopausal status and time since biopsy may modify the risk of breast cancer among women with BBD. In view of the small numbers of some lesions (e.g., radial scar, multiple papilloma, complex fibroadenoma, columnar cell hyperplasia, and atypical hyperplasia) in this and other cohorts, it would be valuable to undertake a pooled analysis of data from existing cohorts of women with biopsy-

confirmed BBD who have been followed for the development of breast cancer, using uniform pathologic criteria.

Acknowledgments

We thank Emily Harris for her contributions to the development of this study, and we also thank Victor Kamensky for his programming and database management support. This study was supported by NIH: RO1-CA95661-01 “p53 in BBD and breast cancer risk: a multicenter cohort.”

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Table 1

Description of the three cohorts of women biopsied for BBD

	Toronto, Canada	**London, UK**	**Portland, USA**
Source	Canadian National Breast Screening Study (NBSS)	Guy's Hospital	Kaiser Permanente Northwest (KPNW)
Cohort definition	Histopathologic dx of BBD in women aged 40–59	Histopathologic dx of BBD in women aged 18–77	Histopathologic dx of BBD in women aged 18–85
Enrollment/recruitment years	1980–1988	1946–1984	1970–1994
Number	4,888	6,494	9,315
Risk factor data	Standardized questionnaires	Medical records	Medical records
Tissue acquisition	Paraffin-embedded blocks obtained from hospitals across Canada	Paraffin-embedded blocks	Paraffin-embedded blocks
Ascertainment of breast cancer	Direct follow-up until 1988: reports of procedures + annual questionnaires sent to study subjects. Thereafter, breast cancer cases were ascertained by record linkage to Canadian cancer incidence and mortality databases	National Health Service Central Register forwarded information on cancer notification of death for cohort members to the study coordinating center	KPNW Cancer Registry
End of follow-up	31/12/1998 to 31/12/2000, depending on the province	31/12/2003	31/12/2001

Table 2

Classification of breast cancer biopsy results of 1,239 women

BBD risk level	Biopsy result/lesion	*n*[a]
Non-proliferative disease/normal pathology	Fibrosis	807
	Cysts	366
	Apocrine metaplasia	527
	Simple fibroadenoma	124
	No lesion	252
Proliferative disease without atypia	Epithelial hyperplasia without atypia	560
	Columnar cell hyperplasia without atypia	124
	Complex fibroadenoma without atypia	52
	Sclerosing adenosis	298
	Radial scar	34
	Papilloma	119
Proliferative disease with atypia	Atypical ductal hyperplasia	19
	Atypical lobular hyperplasia	21
	Atypical columnar hyperplasia	6
	Complex fibroadenoma with atypia	1

[a] BBD lesions may include more than one type

Table 3

Number of cases and controls from each center and exclusions

	Toronto	London	Portland	Total
Number of unique individuals	260	452	613	1,325
Number of controls used an additional 1×	4	0	7	
Number of controls used an additional 2×	0	0	3	
Number of controls that reappear as cases	6	8	6	
Total number of records	270	460	632	1,362
Number of case records	119	230	316	665
Number of control records	151	230	316	697
Exclusions (breast cancer before baseline, no breast tissue, missing pathology data)	1	122	0	123
Case records excluded	0	50	0	50
Control records excluded	1	72	0	73
Total number of records after exclusions (used in unmatched analysis)	269	338	632	1,239
Cases after exclusions	119	180	316	615
Controls after exclusions	150	158	316	624
Total number of women after exclusions	259	332	613	1,204
Total number of case-control sets (used in matched analysis)	101[a]	151[b]	316[b]	568

[a] Includes nine matched triplets (one case and two controls)

[b] Matched pairs only

Table 4

Characteristics of women by histologic grouping of BBD

Characteristic	All women (*n* = 1,239)	Non-proliferative disease/normal pathology[a] (*n* = 440)	Proliferative disease without atypia (*n* = 755)	Proliferative disease with atypia (*n* = 44)
Percentage of total		35.5	60.9	3.6
Age at biopsy				
<40	222 (17.9)	107 (24.3)	109 (14.4)	6 (13.6)
40 to <50	482 (38.9)	167 (38.0)	303 (40.1)	12 (27.3)
50 to <60	332 (26.8)	113 (25.7)	209 (27.7)	10 (22.7)
60 to <70	131 (10.6)	35 (8.0)	85 (11.3)	11 (25.0)
≥70	72 (5.8)	18 (4.1)	49 (6.5)	5 (11.4)
Mean age at biopsy (years)	48.7 ± 11.5	46.7 ± 11.7	49.6 ± 11.1	53.1 ± 11.7
Menopausal status				
Premenopausal	646 (52.1)	242 (55.0)	387 (51.3)	17 (38.6)
Perimenopausal	126 (10.2)	51 (11.6)	71 (9.4)	4 (9.1)
Postmenopausal	467 (37.7)	147 (33.4)	297 (39.3)	23 (52.3)
Family history of breast cancer in a first-degree relative				
No	1002 (80.9)	362 (82.3)	610 (80.8)	30 (68.2)
Yes	192 (15.5)	60 (13.6)	119 (15.8)	13 (29.5)
Missing	45 (3.6)	18 (4.1)	26 (3.4)	1 (2.3)

[a] 367 women had non-proliferative disease and 73 women had normal pathology

Table 5

Risk of breast cancer according to BBD histology

Histology	No. of cases	No. of controls	Unadjusted odds ratio[a]	95% CI	Adjusted odds ratio[b]	95% CI
Non-proliferative[c]	190	250	1.00	Reference	1.00	Reference
Proliferative without atypia	393	362	1.44	1.11–1.87	1.45	1.10–1.90
Proliferative with atypia	32	12	4.73	2.11–10.61	5.27	2.29–12.15
Atypical ductal hyperplasia	13	6	2.50	0.49–12.87	2.69	0.47–15.61
Atypical lobular hyperplasia	16	5	8.00	1.00–63.96	8.13	0.93–71.12
Atypical columnar hyperplasia	5	1	2.00	0.18–22.05	1.42	0.10–20.70
Columnar cell						
Focal	34	37	0.81	0.47–1.39	0.81	0.46–1.43
Multiple	30	21	1.72	0.87–3.41	1.65	0.81–3.36
Complex fibroadenoma w/o atypia	32	20	1.71	0.94–3.10	1.74	0.94–3.22
Radial scar	13	21	0.53	0.24–1.19	0.58	0.25–1.35
Papilloma						
1–2	56	44	1.13	0.74–1.74	1.09	0.70–1.71
Multiple (≥3)	11	8	1.38	0.56–3.44	1.36	0.52–3.51

[a] Based on matched-set analysis (matched on center and age at biopsy)

[b] Matched-set analysis with breast cancer risk factors (age at menarche, age at first live birth, number of pregnancies, menopausal status [premenopausal, perimenopausal, postmenopausal], and family history of breast cancer in a first degree-relative)

[c] Reference group for all odds ratios is women with non-proliferative disease/no pathology

Table 6

Association of BBD histology with breast cancer risk stratified by modifying factors

Modifying factor	Histology	Cases	Controls	Odds ratio	95% CI	*p*-value for interaction
Age						
<50	Non-proliferative disease	118	156	1.00	Reference	
	Proliferative disease w/o atypia	218	194	1.46	1.03–2.08	
	Atypical hyperplasia	14	4	7.54	1.96–29.04	
≥50	Non-proliferative disease	72	94	1.00	Reference	
	Proliferative disease w/o atypia	175	168	1.55	0.95–2.53	
	Atypical hyperplasia	18	8	3.96	1.26–12.40	0.12
Menopausal status						
Premenopausal	Non-proliferative disease	111	131	1.00	Reference	
	Proliferative disease w/o atypia	209	178	1.18	0.79–1.75	
	Atypical hyperplasia	13	4	5.84	1.45–23.58	
Postmenopausal	Non-proliferative disease	60	87	1.00	Reference	
	Proliferative disease w/o atypia	149	148	1.97	1.14–3.42	
	Atypical hyperplasia	16	7	2.54	0.73–8.80	<0.01
Family history of breast cancer in a first-degree relative						
Absent	Non-proliferative disease	147	215	1.00	Reference	
	Any proliferative disease	340	300	2.00	1.42–2.80	
Present	Non-proliferative disease	33	27	1.00	Reference	
	Any proliferative disease	70	62	1.05	0.69–1.61	0.20
Duration of follow-up						
<15 years	Non-proliferative disease	149	62	1.00	Reference	
	Proliferative disease w/o atypia	304	118	2.24	1.21–4.16	
	Atypical hyperplasia	26	3	9.71	1.89–49.76	
≥15 years	Non-proliferative disease	41	188	1.00	Reference	
	Proliferative disease w/o atypia	89	244	1.46	0.74–2.89	
	Atypical hyperplasia	6	9	5.30	0.84–33.42	<0.01