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Breast Cancer Risk by Extent and Type of Atypical Hyperplasia: An Update from the Nurses' Health Studies

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Abstract

Background—Women with atypical hyperplasia (AH) on a benign breast biopsy (BBB) are at increased risk for the development of breast cancer. However, the relationship between type and extent of AH (atypical ductal hyperplasia (ADH) vs. atypical lobular hyperplasia (ALH)) and magnitude of breast cancer risk is not well-defined.

Methods—We conducted a nested case-control study of benign breast disease and breast cancer risk. Women with breast cancer and a prior BBB (cases=488) were matched to women with a prior BBB but free from breast cancer (controls=1907). BBB slides were reviewed and categorized as either non-proliferative, proliferative without atypia, or AH (ADH or ALH). The number of foci of AH was also recorded.

Results—Among women with ADH, the inter-relationship between extent of atypia and breast cancer risk was not significant (OR=3.5; 95%CI 2.2-5.6 for 1-2 foci, OR= 2.7; 95%CI 1.4-5.1 for ≥3 foci; p=0.58). Similarly, while the risk with ALH was higher for those with ≥3 foci than for those with <3 foci, the difference was not statistically significant (OR=5.2; 95%CI 2.7-10.0 for 1-2 foci; OR=8.0; 95%CI 4.5-14.2 for ≥3 foci; p=0.66).

Conclusion—This analysis demonstrates that the extent of ADH or ALH did not significantly contribute to breast cancer risk. The lack of a significant dose-response relationship between extent and type of atypia and breast cancer risk suggests that it would be premature to use extent of atypia to influence management decisions in women with ADH or ALH.

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Keywords

Breast cancer; benign breast disease; atypical hyperplasia

Introduction

The relationship between histologic category of benign breast disease (BBD) and risk of subsequent breast cancer is well established (1-13). Both retrospective cohort studies and case-control studies indicate that women with proliferative lesions without atypia in a benign breast biopsy have a 1.5- to 2-fold increase in breast cancer risk and those with atypical hyperplasia (AH) have a 3- to 5-fold higher risk compared to women with non-proliferative breast lesions (1-15). Recently it has been suggested that a greater extent of atypia, or the presence of multifocality, further elevates breast cancer risk beyond that documented for the mere presence of atypia (16, 17). However, the relationship between the extent of atypia and risk is not well defined.

Benign breast disease is a condition that affects a large number of women and causes a substantial amount of anxiety due to its association with breast cancer. Nearly 20% of women who have annual screening mammograms over a 10-year period will undergo a biopsy (18), and the majority (~80%) of these biopsies will show BBD (19). Given the large number of women undergoing screening mammography and the frequent occurrence of BBD among these women, verification of whether or not the extent of atypia influences breast cancer risk would clearly be of value to assist in risk assessment and clinical management. We, therefore, conducted a nested case-control study among women in the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II) who had a previous diagnosis of benign breast disease in order to evaluate further the association between extent (as defined by the number of foci of AH) and type of atypia (i.e. atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH)) in determining breast cancer risk.

Methods

Study population

The NHS is an ongoing prospective cohort study that began in 1976, when 121,700 female registered nurses between ages 30 and 55 completed a mailed, self-administered questionnaire about their health behaviors, lifestyle factors, and medical histories. Follow-up questionnaires have been sent to participants every two years to obtain updated information. The biennial questionnaires have assessed a variety of known and suspected risk factors for breast cancer, including history of BBD and specifically BBD confirmed by biopsy. Deaths are reported by family members and the postal service, and regular searches of the computerized National Death Index are also conducted (20). The NHS II is a separate cohort study consisting of 116,671 female registered nurses who were between ages 25 and 42 when the study began in 1989. The follow-up methods used in this cohort are very similar to those for the NHS (21). On each biennial questionnaire, participants have been asked if they have ever been diagnosed with BBD and, if yes, whether the diagnosis was confirmed by biopsy. In general, the response rate to each questionnaire has been very similar among

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women who reported a previous diagnosis of BBD and among those who did not. For example, 85% of women who had been diagnosed with BBD as of 1986 completed the 1996 questionnaire, compared to 82% of those who did not report a diagnosis of BBD (22, 23).

Design of nested case-control study

We conducted a nested case-control study of BBD and breast cancer risk among participants in the NHS and NHS II who had reported a previous diagnosis of BBD either requiring hospitalization or confirmed by biopsy. Within this subcohort, eligible cases were women who reported a first diagnosis of breast cancer between 1976 and return of the 1998 questionnaire (NHS) or between 1991 and return of the 1997 questionnaire (NHS II). Self-reported breast cancers were confirmed by review of medical records, and both invasive breast cancer and carcinoma in situ were included in the study. Eligible controls were women who were free from breast cancer at the time the case was diagnosed and who also had a previous diagnosis of biopsy-confirmed BBD; they were matched to cases on age at breast cancer diagnosis or index date (<45, 45-49, 50-54, 55-59, ≥ 60), year of benign breast biopsy (<1970, 1970-79, 1980-89, ≥1990), and follow-up time (continuous years from BBD diagnosis to breast cancer diagnosis or index date). We attempted to identify four matched controls for each case, but this was not always possible for logistical reasons. The study was approved by the Human Research Committee of Brigham and Women's Hospital, Boston, MA.

Collection and review of benign breast biopsy specimens

Cases and controls were contacted for permission to obtain their BBD pathology records and biopsy specimens. Historically, more than 70% of women originally identified for the nested case-control study confirmed the diagnosis and granted permission, and histologic specimens have typically been obtained for >50% of those giving permission. The primary reason given by hospital pathology departments for not sending specimens was that they had been destroyed or were no longer available (35%). Approximately 98% of pathology specimens that were obtained were considered to be of good quality and were evaluated by the study pathologists, resulting in 488 cases and 1907 controls.

Biopsy slides were independently reviewed by one of three pathologists (LCC, SJS or JLC) who were blinded to participants' case or control status. The pathologists completed a detailed worksheet with information on the morphologic features of each specimen, and lesions were then classified as non-proliferative, proliferative without atypia, or atypical hyperplasia according to the criteria developed by Page, et al. (15). All biopsies, including bilateral biopsies, were classified according to the most severe changes present, and specimens with possible or definite atypical hyperplasia were reviewed by a second pathologist. When present, atypia was further categorized as either ADH or ALH according to the aforementioned criteria of Page, et al. (15) and the number of foci of atypia (i.e. terminal duct lobular units and/or ducts involved by the atypical proliferation) was also recorded.

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Statistical analysis

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer risk according to histologic category of BBD, AH subtype, and extent of atypia, using non-proliferative disease as the reference group. We also performed similar analyses jointly classifying women according to both type and extent of atypia. Unconditional, rather than conditional, logistic regression was used because this analytic approach allowed us to use all cases and controls for whom we had histological information. Trend tests for extent of atypia (among all women with AH) were performed.

We first adjusted only for the matching factors, which were age at breast cancer diagnosis or index date (< 45, 45-49, 50-54, 55-59, ≥ 60), year of benign breast biopsy (< 1970, 1970-79, 1980-89, ≥ 1990), and follow-up time (years from BBD diagnosis to breast cancer diagnosis or index date). Adjustment was then made for potential confounding factors, classifying women according to their responses for the questionnaire cycle prior to breast cancer diagnosis or index date. In addition to the matching factors, the following factors were included in the multivariate models: first-degree family history of breast cancer (yes, no), age at menarche (< 12, 12, 13, ≥ 14), parity/age at first birth (nulliparous, one to two children with age at first birth < 25, one to two children with age at first birth 25 to 29, one to two children with age at first birth ≥ 30, three or more children with age at first birth < 25, three or more children with age at first birth ≥ 25), body mass index (< 21, 21 to 22.9, 23 to 24.9, 25 to 29.9, ≥ 30 kg/m^2), menopausal status/type of menopause (premenopausal, natural menopause, bilateral oophorectomy, other or unknown type of menopause), and status/duration of postmenopausal hormone use (never, past, current < 5 years, current ≥ 5 years). Indicator variables were created to represent categories of the matching factors and other covariates, and follow-up time was modeled as a continuous variable. All statistical analyses were performed using the SAS software package (version 8.2; SAS Institute, Cary, NC).

Results

The mean age at benign breast biopsy was 44.2 years for cases (range, 17 to 72 years) and 44.4 years for controls (range, 15 to 73 years), and the median time since biopsy was 8.4 years for cases and 7.7 years for controls. As with prior work from the NHS, we continue to demonstrate a 1.6-fold increase in breast cancer risk associated with proliferative disease without atypia and a 4.5-fold increase in risk associated with a diagnosis of atypical hyperplasia (Table 1). Further, when examined according to type of atypia (ADH vs. ALH), we demonstrate that a greater elevation in risk is conferred by a diagnosis of ALH (OR=6.6, 95% CI 4.2-10.3) compared with ADH (OR=3.2, 95% CI 2.1-4.7; p-heterogeneity=0.006). In the few patients with a combined diagnosis of ADH and ALH (n=16 cases and 17 controls), the OR was similarly elevated at 6.7 (95% CI 3.2-13.9).

When we examined the association between extent of atypia (combined ADH and ALH) and breast cancer risk (Table 2), there appeared to be a trend toward greater breast cancer risk with more foci of atypia (ORs=3.8, 4.5 and 5.3 for 1, 2 and 3 or greater foci of AH, respectively); however, this was not significant (p-trend=0.22). When we examined breast cancer risk according to both type and extent of atypia (Table 3), the extent of atypia was not associated with breast cancer risk for women with ADH (OR=3.5 for 1-2 foci, OR= 2.7

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for ≥3 foci; p =0.41). Similarly, while the risk of breast cancer was higher for women with ALH who had more extensive atypia than those with fewer foci of atypia (OR=5.2 for 1-2 foci; OR=8.0 for ≥3 foci), again this difference was not statistically significant (p=0.19).

Overall, 58.3% of breast cancers occurred in the ipsilateral breast among women with AH, which was greater than that seen for women with non-proliferative disease and proliferative disease without atypia (51.3% and 54.9% respectively) (Table 1). There was no association between laterality of subsequent breast cancer and extent of atypical hyperplasia (p=0.76). Even when stratified according to type and extent of atypia, no significant differences were seen (61.3% vs. 69.2% for 1-2 foci vs. ≥3 foci ADH, p=0.58 and 52.6% vs. 57.7% for 1-2 foci vs. ≥3 foci ALH, p=0.66). Moreover, there was no difference in the proportion of ipsilateral cancers among women with AH vs. women without AH according to time since biopsy: 58.8% of cancers in women with AH occurred in the ipsilateral breast in the first 10 years vs. 57.1% greater than 10 years post biopsy (p-hetereogeneity=0.55 in multivariate models) supporting our observations in prior analyses from the Nurses' Health Study (23).

Discussion

We and others (1-16, 22-24) have shown that among women who have had a benign breast biopsy, the subsequent breast cancer risk varies according to the histologic category of BBD, being moderately increased in women with proliferative lesions without atypia and substantially increased among women with AH. In this analysis, we continue to see the same levels of risk we have reported previously (22, 23). Further, we demonstrate, once again, that the subsequent breast cancer risk associated with atypical lobular hyperplasia is greater than that associated with a diagnosis of atypical ductal hyperplasia (Table 1) (23). Of note, this contrasts with data from the Mayo Benign Breast Disease Cohort in which no significant difference in breast cancer risk was observed by subtype of atypia (RRs=4.8 vs. 3.9 for ALH vs. ADH; p=0.54). (17). However, Zhou et al., in a meta-analysis evaluating breast cancer risk in women with histologically confirmed benign breast disease (2,340 cases and 4,422 controls) (25), demonstrated an odds ratio (OR) of 5.14 for women with ALH (95% CI 3.5-7.5) compared with an OR of 2.9 for women with ADH (95% CI 2.2-4.0), suggesting a difference in the magnitude of risk for these two histopathologically distinct lesions that may be masked by combining ADH and ALH into a single category of AH.

To date, despite potentially important clinical implications given the large number of women diagnosed with BBD, the interrelationship between type and extent of atypia in defining the magnitude of breast cancer risk have not been widely investigated. While we found that among women with AH (with ADH and ALH combined), there appeared to be a relationship between the number of foci of atypia and magnitude of breast cancer risk (Table 2), on further stratification by *type* and extent of atypia, it became apparent that association between extent of atypia and breast cancer risk was being driven by type of atypia, i.e. ALH, rather than extent of atypia (Table 3). Hartmann and colleagues have reported that the extent of atypia is significantly related to the subsequent breast cancer risk with relative risks of 3.2, 5.5 and 7.6 for 1, 2 and 3+ foci of atypical hyperplasia (p<0.001) (16, 17), but these studies did not further stratify by type of atypia. Thus, it is possible that ALH as opposed to extent of atypia may be conferring the greater magnitude of effect seen with increasing foci

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of atypia in that study also. Of note, in the Mayo Benign Breast Disease Cohort, 60% of subjects with AH had 1 focus of atypia and 17% of subjects had 3+ foci compared with 34% and 43% for corresponding categories in the Nurses' Health Studies, which would likely magnify any effect extent of atypia, if real, in the NHS. It is possible that the difference in mean number of slides reviewed per subject (3.2 for Mayo (16) vs. 4.5 for NHS) may also have contributed to the greater proportion of women with a single focus of atypia in the Mayo Cohort compared with the current study and again should argue for a magnified effect of extent of atypia in the NHS compared with the Mayo Cohort.

More recent studies have emphasized the slight excess of ipsilateral cancers occurring following a diagnosis of AH (16, 17, 22). The preponderance of ipsilateral cancers would suggest that at least some of these lesions may be behaving as precursor lesions rather than as indicators of a bilaterally increased breast cancer risk, but our ability to determine which lesions might behave as precursors remains a challenge. From a management perspective, it is appropriate to continue to manage patients with a breast biopsy diagnosis of AH as having a generalized increase in breast cancer risk.

A potential limitation to our study is that we were unable to obtain for review pathology material on a proportion of eligible cases and controls who had given permission. However, the primary reason for not being able to obtain specimens was the routine disposal of biopsy material by the hospitals; therefore, this is unlikely to have introduced selection bias into the study. Notable strengths are the consistent histopathologic review by expert breast pathologists and the high level of response by study participants to biennial questionnaires reporting epidemiologic factors.

In conclusion, any apparent association between number of foci of AH and a higher risk of subsequent breast cancer was eliminated when extent and subsequent breast cancer risk was stratified by type of atypia. Our data further suggest that any indication of association by extent of atypia appears to be driven by the greater risk associated with ALH (OR=6.6 vs. 3.2 for ADH; p-het=0.006). Given our findings, extent of ADH or ALH should not influence management decisions for individual patients in which these lesions are the most significant finding on benign breast biopsy. In particular, there is no evidence that women with a greater extent of ADH should be managed as women with ductal carcinoma in situ.

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References

1. Kodlin D, Winger EE, Morgenstern NL, Chen U. Chronic mastopathy and breast cancer. A follow-up study. Cancer. 1977; 39(6):2603–7. [PubMed: 872059]
2. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med. 1985; 312(3):146–51. [PubMed: 3965932]
3. Carter CL, Corle DK, Micozzi MS, Schatzkin A, Taylor PR. A prospective study of the development of breast cancer in 16,692 women with benign breast disease. Am J Epidemiol. 1988; 128(3):467–77. [PubMed: 3414655]
4. Tavassoli FA, Norris HJ. A comparison of the results of long-term follow-up for atypical intraductal hyperplasia and intraductal hyperplasia of the breast. Cancer. 1990; 65(3):518–29. [PubMed: 2297643]
5. Palli D, Rosselli del Turco M, Simoncini R, Bianchi S. Benign breast disease and breast cancer: a case-control study in a cohort in Italy. Int J Cancer. 1991; 47(5):703–6. [PubMed: 2004851]
6. London SJ, Connolly JL, Schnitt SJ, Colditz GA. A prospective study of benign breast disease and the risk of breast cancer. JAMA. 1992; 267(7):941–4. [PubMed: 1734106]
7. Krieger N, Hiatt RA. Risk of breast cancer after benign breast diseases. Variation by histologic type, degree of atypia, age at biopsy, and length of follow-up. Am J Epidemiol. 1992; 135(6):619–31. [PubMed: 1580238]
8. McDivitt RW, Stevens JA, Lee NC, Wingo PA, Rubin GL, Gersell D. Histologic types of benign breast disease and the risk for breast cancer. The Cancer and Steroid Hormone Study Group. Cancer. 1992; 69(6):1408–14. [PubMed: 1540878]
9. Dupont WD, Parl FF, Hartmann WH, Brinton LA, Winfield AC, Worrell JA, et al. Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer. 1993; 71(4):1258–65. [PubMed: 8435803]
10. Bodian CA, Perzin KH, Lattes R, Hoffmann P, Abernathy TG. Prognostic significance of benign proliferative breast disease. Cancer. 1993; 71(12):3896–907. [PubMed: 8389654]
11. Marshall LM, Hunter DJ, Connolly JL, Schnitt SJ, Byrne C, London SJ, et al. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev. 1997; 6(5):297–301. [PubMed: 9149887]
12. Shaaban AM, Sloane JP, West CR, Moore FR, Jarvis C, Williams EM, et al. Histopathologic types of benign breast lesions and the risk of breast cancer: case-control study. Am J Surg Pathol. 2002; 26(4):421–30. [PubMed: 11914619]
13. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, et al. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005; 353(3):229–37. [PubMed: 16034008]
14. Fitzgibbons PL, Henson DE, Hutter RV. Benign breast changes and the risk for subsequent breast cancer: an update of the 1985 consensus statement. Cancer Committee of the College of American Pathologists. Arch Pathol Lab Med. 1998; 122(12):1053–5. [PubMed: 9870852]
15. Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer. 1985; 55(11):2698–708. [PubMed: 2986821]
16. Degnim AC, Visscher DW, Berman HK, Frost MH, Sellers TA, Vierkant RA, et al. Stratification of breast cancer risk in women with atypia: a Mayo cohort study. J Clin Oncol. 2007; 25(19): 2671–7. [PubMed: 17563394]
17. Hartmann LC, Radisky DC, Frost MH, Santen RJ, Vierkant RA, Benetti LL, et al. Understanding the premalignant potential of atypical hyperplasia through its natural history: a longitudinal cohort study. Cancer Prev Res (Phila). 2014; 7(2):211–7. [PubMed: 24480577]
18. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations [see comments]. N Engl J Med. 1998; 338(16):1089–96. [PubMed: 9545356]
19. Menes TS, Rosenberg R, Balch S, Jaffer S, Kerlikowske K, Miglioretti DL. Upgrade of high-risk breast lesions detected on mammography in the Breast Cancer Surveillance Consortium. Am J Surg. 2014; 207(1):24–31. [PubMed: 24112677]
20. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, et al. Test of the National Death Index. Am J Epidemiol. 1984; 119(5):837–9. [PubMed: 6720679]

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21. Colditz GA. The Nurses' Health Study: Findings during 10 years of follow-up of a cohort of U.S. women. Curr Probl Obstet Gynecol Fertil. 1990; 13:129–74.

22. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. The influence of family history on breast cancer risk in women with biopsy-confirmed benign breast disease: results from the Nurses' Health Study. Cancer. 2006; 107(6):1240–7. [PubMed: 16902983]

23. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. Cancer. 2007; 109(2):180–7. [PubMed: 17154175]

24. Kabat GC, Jones JG, Olson N, Negassa A, Duggan C, Ginsberg M, et al. A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer. Cancer Causes Control. 2010; 21(6):821–8. [PubMed: 20084540]

25. Zhou WB, Xue DQ, Liu XA, Ding Q, Wang S. The influence of family history and histological stratification on breast cancer risk in women with benign breast disease: a meta-analysis. Journal of cancer research and clinical oncology. 2011; 137(7):1053–60. [PubMed: 21499874]

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Table 1

Odds Ratios and 95% Confidence Intervals (CIs) for Breast Cancer Risk According to Histologic Subtype of Benign Breast Disease (BBD) among Participants with BBD in the Nurses' Health Study (1976-1998) and Nurses' Health Study II (1991-1997)

	Cases (n=488)	Percent ipsilateral*	Controls (n=1907)	OR (95%CI)**
BBD Histologic Subtype				
Nonproliferative	108	51.3	680	1.0 (reference)
Proliferative without Atypia	256	54.9	1035	1.6 (1.3-2.1)
All Atypical Hyperplasia	124	58.3	192	4.5 (3.2-6.2)
Atypical Ductal Hyperplasia (ADH)	53	62.2	120	3.2 (2.1-4.7)
Atypical Lobular Hyperplasia (ALH)	55	55.1	55	6.6 (4.2-10.3)
ADH and ALH	16	55.6	17	6.7 (3.2-13.9)

p-het, ADH vs. ALH=0.006

*Among cases with available laterality data (N=387).

**Adjusted for matching factors (age at breast cancer diagnosis, year of benign breast biopsy, and time since BBD biopsy) and family history of breast cancer, age at menarche, parity/age at first birth, body mass index, menopausal status/type of menopause, and duration of postmenopausal hormone use.

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Table 2

Odds ratios (ORs) and 95% confidence intervals (CI) for breast cancer risk according to histologic subtype of benign breast disease and extent of atypia among participants in the Nurses' Health Study (1976-1998) and Nurses' Health Study II (1991-1997)

	Cases	Percent Ipsilateral*	Controls	OR (95% CI)
BBD Histologic Subtype and extent of atypia				
Non-proliferative	108	51.3	680	1.0 (ref)
Proliferative without atypia	256	54.9	1035	1.6 (1.3-2.1)
AH, 1 focus†	37	62.5	66	3.8 (2.4-6.1)
AH, 2 foci	26	54.6	42	4.5 (2.6-7.7)
AH, ≥3 foci	56	59.1	74	5.3 (3.5-8.1)

** Adjusted for matching factors (age at breast cancer diagnosis, year of benign breast biopsy, and time since BBD biopsy) and family history of breast cancer, age at menarche, parity/age at first birth, body mass index, menopausal status/type of menopause, and duration of postmenopausal hormone use.

p-trend, number of foci of AH = 0.22

*Among cases with available laterality data (N=387).

†Number of cases/controls included in foci analysis (119 cases, 182 controls) does not add up to total number of cases/controls with AH (124 cases, 192 controls) due to missing foci information.

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Table 3

Odds ratios (ORs) and 95% confidence intervals (CI) for breast cancer risk according to histologic subtype of benign breast disease and type and extent of atypia among participants in the Nurses' Health Study (1976-1998) and Nurses' Health Study II (1991-1997)

BBD Histologic Subtype and type and extent of atypia	Cases	Percent Ipsilateral*	Controls	OR (95% CI)
Non-proliferative	108	51.3	680	1.0 (ref)
Proliferative without atypia	256	54.9	1035	1.6 (1.3-2.1)
ADH, 1-2 foci	37	61.3	75	3.5 (2.2-5.6)
ADH, ≥3 foci	15	69.2	41	2.7 (1.4-5.1)
ALH, 1-2 foci	19	52.6	25	5.2 (2.7-10.0)
ALH, ≥3 foci	32	57.7	26	8.0 (4.5-14.2)

** Adjusted for matching factors (age at breast cancer diagnosis, year of benign breast biopsy, and time since BBD biopsy) and family history of breast cancer, age at menarche, parity/age at first birth, body mass index, menopausal status/type of menopause, and duration of postmenopausal hormone use.

Age-adjusted p-value for difference in laterality: ADH 1-2 vs. ≥3 foci, p=0.58; ALH 1-2 vs. ≥3 foci, p=0.66

p-het for breast cancer risk (not laterality):

p-het (age-adjusted), ADH 1-2 vs. ≥3 foci=0.41; p-het (age-adjusted), ALH 1-2 vs. ≥3 foci=0.19

p-trend (age-adjusted), number of AH foci among those with ADH = 0.54; p-trend (age-adjusted), number of AH foci among those with ALH = 0.24

*Among cases with available laterality data (N=387).