Published in final edited form as:
Cancer. 2009 April 1; 115(7): 1404–1411. doi:10.1002/cncr.24167.

Lobule Type and Subsequent Breast Cancer Risk: Results from the Nurses' Health Studies

Heather J. Baer, ScD[1,2], **Laura C. Collins, MD**[3], **James L. Connolly, MD**[3], **Graham A. Colditz, MD, DrPH**[4], **Stuart J. Schnitt, MD**[3], and **Rulla M. Tamimi, ScD**[2,5]

[1] Division of General Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[2] Department of Epidemiology, Harvard School of Public Health, Boston, MA

[3] Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

[4] Department of Surgery, Washington University School of Medicine, St. Louis, MO

[5] Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

Background—Lobules in normal breast tissue can be classified based on their degree of development, which may affect their susceptibility to carcinogenesis; few epidemiologic studies, however, have addressed this.

Methods—We examined the association between lobule type and subsequent breast cancer risk in a nested case-control study of benign breast disease (BBD) and breast cancer within the Nurses' Health Studies (200 cases, 915 controls). Benign breast biopsy slides were reviewed by pathologists, and normal terminal duct lobular units were classified as having no type 1 lobules, mixed lobule types, or predominant type 1 and no type 3 lobules. Logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI) for the association between lobule type and breast cancer risk.

Results—Women with predominant type 1 and no type 3 lobules (54 cases, 321 controls) had a decreased risk of breast cancer compared to those with no type 1 lobules or mixed lobule types (OR = 0.63, 95% CI = 0.44–0.91), although this was attenuated after adjustment for histologic category of BBD (OR = 0.71, 95% CI = 0.49–1.02). Having predominant type 1 lobules and no type 3 lobules was associated with a similar risk reduction for all categories of BBD (nonproliferative: OR = 0.73, 95% CI: 0.36–1.50; proliferative without atypia: OR = 0.80, 95% CI = 0.47–1.35; atypical hyperplasia: OR = 0.61, 95% CI: 0.28–1.35).

Conclusions—These results provide preliminary evidence that lobule type may be an important marker of breast cancer risk in women with BBD.

Keywords

benign breast disease; breast cancer; lobule type; differentiation; involution

Address for correspondence and reprints: Heather J. Baer, Brigham and Women's Hospital, Division of General Medicine, 1620 Tremont Street, 3rd floor, Boston, MA 02120, Phone: 617-525-7503, Fax: 617-732-7072, E-mail: hbaer@partners.org.

The authors have no financial disclosures.

INTRODUCTION

The lobules of the breast can be classified into four distinct types, reflecting different stages of morphologic development. Type 1 lobules are the least developed and are present in the immature female breast prior to menarche, whereas type 3 lobules are the most fully developed and are usually seen in the breasts of women under hormonal stimulation or during pregnancy. Type 2 lobules evolve from type 1 lobules and are intermediate in their degree of differentiation. The breasts of nulliparous women are composed mainly of type 1 lobules, although occasional types 2 and 3 lobules are present; in contrast, type 3 lobules are the predominant structure in parous women. Type 4 lobules are present only during lactation and then regress back to type 3 lobules.1

It has been hypothesized that the degree of lobular differentiation may affect the susceptibility of breast tissue to carcinogenesis, and that the long-term protective effect of pregnancy on breast cancer risk may be attributable to the greater degree of development of the lobules in parous women.1 This is supported by experimental evidence showing that rats exposed to a chemical carcinogen before the first pregnancy are more likely to develop mammary tumors compared to rats exposed to the same carcinogen after pregnancy and lactation.2, 3 Although these studies suggest that breast carcinogenesis is inversely related to the degree of lobular development in animal models, it is unclear if an analogous situation exists in the human breast. To our knowledge, only one formal epidemiologic study has examined this, and it did not find any association between lobule type and breast cancer risk; 4 however, there were several design considerations that make the results difficult to interpret.

In addition, breast tissue in women undergoes age-related lobular involution, which is characterized by a reduction in the amount of glandular tissue. During the involution process, type 2 and type 3 lobules regress back to type 1 lobules; consequently, after menopause, both parous and nulliparous women have breasts with a preponderance of type 1 lobules and relatively few type 3 lobules. Although this is a normal process with a predictable series of changes occurring in the lobules, the degree and rate of involution vary among individual women, and it has been hypothesized that more complete involution may be protective against the development of breast cancer.5, 6 In fact, in a recent retrospective cohort study, lobular involution was associated with decreased risk of breast cancer among women with previous benign breast disease (BBD), and this was apparent for all histologic categories of BBD.7

This finding has led to the hypothesis that type 1 lobules in parous women, most of which probably were type 3 lobules that have undergone involution, may be biologically different than immature type 1 lobules in nulliparous women and exhibit different susceptibilities to carcinogenesis.8 Understanding the relation between lobule type and breast cancer risk could have important clinical implications, both in terms of predicting risk for individual women and developing physiologic approaches to prevention.1, 9 The purpose of this study, therefore, was to examine the relation between lobule type and subsequent breast cancer risk, utilizing data from an established case-control study of BBD and breast cancer within the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II).

MATERIALS AND 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. On the 1976, 1978, and 1980 questionnaires, participants were asked if they had ever been diagnosed with fibrocystic or other benign breast disease and whether this diagnosis had required hospitalization; from 1982 onward, the questionnaires have inquired specifically about 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.10 The NHS II is a separate cohort study consisting of 116,609 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 original NHS. 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 or aspiration. The follow-up rate for each two-year cycle has been greater than 90% of the original cohorts, and the total active follow-up through the current cycle is 94.4% for the NHS and 95.3% for the NHS II.

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 that was confirmed by biopsy. Within this subcohort, eligible cases were women who reported a first diagnosis of breast cancer between 1976 and return of the 1996 questionnaire in the NHS or between 1989 and return of the 1995 questionnaire in the 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 completed the questionnaire for the same year that the breast cancer case was reported and had a previous diagnosis of biopsy-confirmed BBD, but were free from breast cancer; they were matched to breast cancer cases on year of birth and year of diagnosis of BBD. We attempted to identify four matched controls for each case, but this was not always possible for logistical reasons. Informed consent was obtained from all participants. The study was approved by the Human Research Committee of Brigham and Women's Hospital, Boston, MA.

Benign Breast Biopsy Specimens

Eligible cases and controls were contacted for permission to obtain their BBD pathology records and biopsy specimens, and specimens then were obtained from hospital pathology departments when possible. These methods have been described in detail elsewhere.11, 12 Briefly, more than 70% of the 1310 cases and 5273 controls who originally were identified for the study confirmed the diagnosis and granted permission, and specimens subsequently were obtained for 52% of those who had granted their permission (465 cases and 1939 controls). The primary reason given by hospital pathology departments for not sending specimens was that they had been destroyed or were no longer available (35%).11, 12

Biopsy slides were independently reviewed by one of two study pathologists (SJS, 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 biopsies were then classified as nonproliferative, proliferative without atypia, or atypical hyperplasia, according to the criteria of Page et al.,13, 14 which have been used in previous investigations in this cohort.12, 15, 16 All biopsies, including bilateral biopsies, were classified according to the most severe changes present, and specimens with possible or definite atypical hyperplasia were jointly reviewed by both pathologists. After excluding participants whose benign biopsy specimens were of poor quality or had no breast tissue, evidence of carcinoma in situ or invasive carcinoma, invalid dates of diagnosis, or

insufficient information on laterality, there were a total of 395 cases and 1610 controls.[11, 12]

Information on lobule type was collected on the benign breast biopsy worksheet for breast cancer cases whose diagnosis was reported on the 1988 through 1994 questionnaires in the NHS or on the 1991 through 1995 questionnaires in the NHS II (n=229), and for matched controls from these same cycles (n=1004). Lobules were classified according to the criteria of Russo and Russo, based on the number of acini per lobule.1 Type 1 lobules were composed of fewer than 12 acini, type 2 lobules were composed on average of approximately 50 acini, and type 3 lobules were composed on average of approximately 80 acini. The study pathologists assessed the presence of any type 1 and any type 3 lobules in normal terminal duct lobular units for each participant. In addition, each participant's predominant lobule type was classified as type 1, type 2, or type 3. For this analysis, women were grouped into three categories: no type 1 lobules, predominant type 1 and no type 3 lobules, and mixed lobule types (all others). The final sample for this analysis included 200 cases and 915 controls who had adequate tissue sections to be categorized by lobule type.

Statistical Analysis

The distributions of breast cancer risk factors were examined according to lobule type among the controls, adjusting for age at benign biopsy when appropriate. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer risk according to categories of lobule type. 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 time since benign biopsy (years from BBD diagnosis to the breast cancer diagnosis or index date, as a continuous variable). Adjustments then were made for potential confounding factors, including first-degree family history of breast cancer (yes, no), age at menarche (< 12, 12, 13, ≥ 14), parity (nulliparous, one to two children, three to four children, five or more children), age at first birth (< 25, 25 to 29, ≥ 30), body mass index (< 21, 21 to 22.9, 23 to 24.9, 25 to 29.9, ≥ 30 kg/m^2), menopausal status (premenopausal, postmenopausal, dubious/unsure), type of menopause (natural, bilateral oophorectomy, other), age at menopause (< 45 years, 45 to 49 years, 50 to 54 years, ≥ 55 years), and postmenopausal hormone use (never, past, current < 5 years, current ≥ 5 years). Accuracy and reproducibility of self-report of natural menopause and ovarian surgery,17 as well as other risk factors,18 have been previously validated in the NHS cohort. Because adjustment for these covariates – either individually or simultaneously in one multivariate model – did not substantially alter the estimates for lobule type but increased the confidence intervals, they were not included in the final models.

In another set of models, additional adjustment was made for histologic category of BBD (nonproliferative, proliferative with no atypia, or atypical hyperplasia), which is a strong predictor of breast cancer risk.14 We also stratified by histologic category and jointly classified women according to histologic category and lobule type, to examine whether the association of lobule type with breast cancer risk differed by category of BBD; a likelihood ratio test was used to test for interaction. All statistical analyses were performed using the SAS software package (version 9.1; SAS Institute, Cary, NC). All tests were two-sided, with $P < 0.05$ indicating statistical significance.

RESULTS

The mean age of benign biopsy among all participants was 44.6 years (range = 15 to 71), and the mean time since biopsy was 9.7 years (range = 0.5 to 42). Compared to women with no type 1 lobules, women with predominant type 1 and no type 3 lobules were older at the

time of their benign breast biopsies, had their biopsies in later years, and had less time since their biopsies (Table 1). There were few significant differences in the distributions of risk factors after adjustment for age at benign biopsy, although women with predominant type 1 lobules and no type 3 lobules had slightly lower parity and younger age at menopause compared to the other types. In addition, histologic category of BBD was associated with lobule type, with a greater percentage of women with predominant type 1 and no type 3 lobules having nonproliferative BBD and a smaller percentage having proliferative BBD without atypia, compared to the other types.

In the multivariate logistic regression models adjusting for the matching factors (Table 2), women with mixed lobule types had similar breast cancer risk compared to those with no type 1 lobules (OR = 1.18, 95% CI: 0.73–1.92), although there was a nonsignificant decrease in risk for women with predominant type 1 and no type 3 lobules (OR = 0.73, 95% CI: 0.42–1.27). Because there was no significant difference in risk between women with mixed lobule types and women with no type 1 lobules, we combined them and used this as the reference group for subsequent analyses. Compared to all other types, women with predominant type 1 and no type 3 lobules had significantly lower risk of breast cancer (OR = 0.63, 95% CI: 0.44–0.91). The decrease in risk was somewhat attenuated after additional adjustment for histologic category of BBD (OR = 0.71, 95% CI: 0.49–1.02), although it was still apparent. The association was similar, although slightly less strong, when only invasive breast cancer cases were included; after adjustment for histologic category of BBD, the OR for women with predominant type 1 and no type 3 lobules was 0.79 (95% CI: 0.53–1.19).

It is plausible that the relation between lobule type and breast cancer risk might be stronger among parous women, because type 1 lobules would be more likely to represent type 3 lobules that already have undergone age-related involution, rather than immature lobules that never went through the full development process.1 To explore this, we conducted a secondary analysis in which we restricted the sample to participants who were parous at the time of their benign biopsy (179 cases, 834 controls). The results were similar to those from the main analysis, with a decrease in risk for women with predominant type 1 and no type 3 lobules compared to women with all other lobule types combined (OR with adjustment for histologic category of BBD = 0.77, 95% CI = 0.52–1.13).

The decrease in risk for women with predominant type 1 and no type 3 lobules, compared to women with all other lobule types combined, was similar for women with nonproliferative BBD (OR = 0.73, 95% CI: 0.36–1.50), proliferative lesions without atypia (OR = 0.80, 95% CI = 0.47–1.35), and atypical hyperplasia (OR = 0.61, 95% CI: 0.28–1.35), and there was no significant interaction between lobule type and histologic category of BBD (P = 0.67) (Table 3). When women were jointly classified according to histologic category and lobule type (Table 4), women who had nonproliferative BBD with predominant type 1 and no type 3 lobules were at the lowest risk (OR = 0.80, 95% CI: 0.41–1.54), and women who had atypical hyperplasia with no type 1 lobules or with mixed lobule types were at the highest risk (OR = 4.76, 95% CI = 2.67–8.48), compared to women with nonproliferative BBD and no type 1 lobules or with mixed lobule types. The odds ratio comparing these two categories (atypical hyperplasia with no type 1 lobules or with mixed lobule types vs. nonproliferative with predominant type 1 and no type 3 lobules) was 5.99 (95% CI: 3.10–11.55).

DISCUSSION

In this established nested case-control study of benign breast disease and breast cancer, women with predominant type 1 and no type 3 lobules had a reduction in breast cancer risk compared to women with all other lobule types, even after adjustment for histologic category of BBD. Some decrease in risk was observed for all categories of BBD, although

the stratified analyses were limited by small numbers of cases and controls. These results suggest that having a larger proportion of type 1 lobules and no type 3 lobules may be protective against the development of breast cancer among women who have had BBD, regardless of their histologic category. Therefore, evaluation of lobule type in the background breast tissue of women who have had a benign breast biopsy may provide additional information about their subsequent risk of breast cancer.

The types of lobules and the stages of lobular development have been well-characterized in animal models, and there is substantial experimental evidence in rodents indicating that the degree of lobular development may be an important determinant of breast cancer risk;[1–3] however, there are very limited data on this subject in humans.[19, 20] To our knowledge, only one previous epidemiologic study has formally examined the association between lobule type and breast cancer risk; that study found no association between predominant lobule type and breast cancer risk.[4] Several design considerations may influence the interpretation of that study. It was a cross-sectional study that assessed lobule type after diagnosis of breast cancer, which may not reflect lobule type prior to cancer development. Another methodologic concern is that cases were age-matched to controls with benign biopsies, yet there was no adjustment for age in the analysis; this could have attenuated any association between lobule type and breast cancer risk (since age is strongly associated with lobule type). In addition, the categories used for lobule type in the previous study were predominant type 1, type 2, and type 3. In the present study, we assessed predominant lobule type as well as the presence of any type 1 or any type 3 lobules, which may have increased the reliability of the assessment and enhanced the amount of contrast between the extreme categories.

Although we did not directly assess the degree of lobular involution in this study, the older age among women with predominant type 1 and no type 3 lobules (mean = 49.1 years) compared to women with no type 1 lobules (mean = 37.1 years) and women with mixed lobule types (mean = 43.5 years) indicates that this group may represent women who have undergone more age-related lobular involution, where type 3 lobules regress back to type 1 lobules. In a recent study from the Mayo Benign Breast Disease cohort that included biopsy specimens from 8736 women with BBD, degree of involution was inversely associated with breast cancer risk; the relative risks were 1.88 (95% CI: 1.59–2.21) for women with no involution, 1.47 (95% CI: 1.33–1.61) for those with partial involution, and 0.91 (95% CI: 0.75–1.10) for those with complete involution, compared to age-matched women with no BBD in the general population.[7] Our study, which assessed lobule type rather than degree of involution, arrived at a similar conclusion – i.e., that women with a larger proportion of type 1 lobules and no type 3 lobules, whose breasts probably have undergone more complete involution, seem to have to have lower breast cancer risk.

The biologic mechanisms by which having a greater proportion of type 1 lobules (among middle-aged, predominantly parous women) or a greater degree of lobular involution may protect against breast cancer development are not well understood. One plausible explanation is that lobular involution leads to a reduction in the total amount of epithelial tissue available for malignant transformation.[6, 7, 9] Other suggested theories are that failure of breast tissue to undergo timely or appropriate involution allows prolonged exposure of epithelial cells to potential carcinogens, or that persistence of type 3 lobules is a marker or phenotype reflecting underlying susceptibility of epithelial or stromal cells to carcinogenesis.[7] Most recently, Russo has proposed that type 1 lobules in early postmenopausal parous women are composed of a different variety of stem cell (Stem cells 2) than immature type 1 lobules in nulliparous women (Stem cells 1), and that Stem cells 2 have a specific genomic signature that renders them refractory to transformation.[8] More in-depth studies of the molecular, genetic, and histopathologic characteristics of the different

lobule types in women at different stages of life are needed to help disentangle these mechanisms.

Our study has several limitations. First, because lobule type was not assessed in all follow-up cycles, we were able to conduct this analysis only among a subset of all participants, which reduced the number of available cases and controls for the analysis and, therefore, the statistical power of the study. Furthermore, because lobule type was not assessed until the 1988 follow-up cycle in the NHS, women with data on lobule type were older at the time of the benign breast biopsy (44.7 years vs. 42.6 years, $p < 0.0001$) and at the breast cancer diagnosis or index date (54.4 vs. 52.9 years, $p = 0.0001$) compared to those who were missing this information. This could potentially affect the generalizibility of the findings if the association of lobule type with breast cancer risk varies with age or other age-related characteristics.

Another limitation is that we did not have data on the reliability of our assessment of lobule type. It is possible that predominant lobule type in normal TDLUs from benign breast biopsy specimens may not be representative of predominant lobule type in the rest of the breast, given the small amount of tissue in some of these specimens. However, a recent study showed a high intraclass correlation for the extent of involution in different quadrants of breast tissue within the same woman, suggesting that lobular involution is a homogenous process.21 Even so, there is likely to have been some misclassification, which could attenuate an association between lobule type and breast cancer risk. Because the pathologists were blinded to case-control status, any misclassification would be unrelated to the outcome. In addition, breast cancer is heterogeneous, and due to the small sample size, we were unable to examine whether there were differences in the associations for lobule type according to specific tumor characteristics such as hormone receptor status. However, within the main NHS cohort, the overall association between BBD and breast cancer risk did not vary according to the estrogen or progesterone receptor status of the tumors,22 suggesting that a non-hormonal mechanism may be involved. The strengths of the study include its prospective design, the confirmation of breast cancer cases through review of medical records, the centralized pathology review of specimens from benign biopsies prior to the development of breast cancer, and the detailed information on other breast cancer risk factors.

In summary, the results from this study indicate that women with predominant type 1 lobules and no type 3 lobules may have a decreased risk of breast cancer compared to all other types combined, providing preliminary evidence that lobule type may be an important marker of breast cancer risk in women with BBD. These findings, which need to be confirmed in larger studies and other populations, could have valuable clinical implications in terms of predicting risk and developing physiologic strategies for prevention.

Acknowledgments

Supported by Public Health Service Grants CA087969, CA046475, and CA050385 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

References

1. Russo J, Russo IH. Toward a physiological approach to breast cancer prevention. Cancer Epidemiol Biomarkers Prev. 1994; 3(4):353–64. [PubMed: 8061586]
2. Russo J, Gusterson BA, Rogers AE, Russo IH, Wellings SR, van Zwieten MJ. Comparative study of human and rat mammary tumorigenesis. Lab Invest. 1990; 62(3):244–78. [PubMed: 2107367]
3. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat. 1982; 2(1):5–73. [PubMed: 6216933]

4. Ramakrishnan R, Gann PH, Wiley EL, Khurana KK, Khan SA. Normal breast lobular architecture in breast biopsy samples from breast cancer cases and benign disease controls. Breast Cancer Res Treat. 2004; 86(3):259–68. [PubMed: 15567942]
5. Henson DE, Tarone RE. On the possible role of involution in the natural history of breast cancer. Cancer. 1993; 71(6 Suppl):2154–6. [PubMed: 8443765]
6. Henson DE, Tarone RE. Involution and the etiology of breast cancer. Cancer. 1994; 74(1 Suppl): 424–9. [PubMed: 8004616]
7. Milanese TR, Hartmann LC, Sellers TA, Frost MH, Vierkant RA, Maloney SD, et al. Age-related lobular involution and risk of breast cancer. J Natl Cancer Inst. 2006; 98(22):1600–7. [PubMed: 17105983]
8. Russo J, Balogh GA, Chen J, Fernandez SV, Fernbaugh R, Heulings R, et al. The concept of stem cell in the mammary gland and its implication in morphogenesis, cancer and prevention. Front Biosci. 2006; 11:151–72. [PubMed: 16146722]
9. Henson DE, Tarone RE, Nsouli H. Lobular involution: the physiological prevention of breast cancer. J Natl Cancer Inst. 2006; 98(22):1589–90. [PubMed: 17105976]
10. 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]
11. 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]
12. 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]
13. 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]
14. Schnitt, SJ.; Connolly, JL. Pathology of benign breast disorders. In: Harris, JR.; Lippman, ME.; Morrow, M.; Osborne, CK., editors. Diseases of the Breast. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.
15. 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]
16. 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]
17. Colditz GA, Stampfer MJ, Willett WC, Stason WB, Rosner B, Hennekens CH, et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. Am J Epidemiol. 1987; 126(2):319–25. [PubMed: 3605058]
18. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Am J Epidemiol. 1986; 123(5):894–900. [PubMed: 3962971]
19. Russo J, Lynch H, Russo IH. Mammary gland architecture as a determining factor in the susceptibility of the human breast to cancer. Breast J. 2001; 7(5):278–91. [PubMed: 11906437]
20. Russo J, Romero AL, Russo IH. Architectural pattern of the normal and cancerous breast under the influence of parity. Cancer Epidemiol Biomarkers Prev. 1994; 3(3):219–24. [PubMed: 8019370]
21. Vierkant RA, Hartmann LC, Pankratz VS, Anderson SS, Radisky D, Frost MH, et al. Lobular involution: localized phenomenon or field effect? Breast Cancer Res Treat. 2008
22. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst. 2004; 96(3):218–28. [PubMed: 14759989]

Table 1

Characteristics of controls* according to lobule type among participants in the Nurses' Health Study (1988–1994) and the Nurses' Health Study II (1991–1995)

	No type 1 lobules	Mixed lobule types	Predominant type 1 and no type 3 lobules	P value
Number controls (%)	125 (13.7)	469 (51.3)	321 (35.1)	
Means				
Age at benign biopsy, yrs	37.1	43.5	49.1	< 0.0001†
Year of benign biopsy (median)	1977	1982	1985	< 0.0001†
Time since benign biopsy, yrs	13.9	9.7	8.0	< 0.0001†
Number benign biopsy slides ‡	5.3	4.7	4.8	0.44
Age at menarche, yrs ‡	12.7	12.6	12.6	0.73
Body mass index, kg/m^2 ‡	24.3	25.1	25.7	0.09
Alcohol intake, g/day ‡	3.8	3.8	3.7	0.97
Parity (parous only) ‡	3.4	3.0	2.7	0.001
Age at first birth, yrs (parous only) ‡	25.0	24.7	24.9	0.09
Age at menopause, yrs (postmenopausal only) ‡	51.2	49.6	47.8	0.001
Percentages				
Premenopausal ‡	30.4	36.1	32.5	0.01
Parous ‡	91.5	93.0	87.6	0.09
First degree family history of breast cancer ‡	15.9	16.1	16.9	0.86
Histologic category of BBD ‡				
Nonproliferative	37.2	29.3	43.7	< 0.0001
Proliferative with no atypia	55.0	58.1	47.6	0.01
Atypical hyperplasia	7.8	12.7	8.7	0.33

*Unless otherwise indicated, all variables refer to the time period immediately prior to the index date.

†P values from analysis of variance models (ANOVA).

‡Means and percentages standardized to the age distribution of controls at the time of benign biopsy, in 5-year categories. Age-adjusted p-values from linear regression models for means and logistic regression models for percentages.

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for lobule type and breast cancer risk among participants in the Nurses' Health Study (1988–1994) and Nurses' Health Study II (1991–1995)

	Cases	Controls	OR (95% CI)*	Adjusted OR (95% CI) †
All women				
No type 1 lobules	26	125	1.0 (REF)	1.0 (REF)
Mixed lobule types	120	469	1.18 (0.73–1.92)	1.10 (0.67–1.80)
Predominant type 1 and no type 3 lobules	54	321	0.73 (0.42–1.27)	0.76 (0.44–1.34)
No type 1 lobules or mixed lobule types	146	594	1.0 (REF)	1.0 (REF)
Predominant type 1 and no type 3 lobules	54	321	0.63 (0.44–0.91)	0.71 (0.49–1.02)
Parous at time of benign breast biopsy				
No type 1 lobules	22	112	1.0 (REF)	1.0 (REF)
Mixed lobule types	107	433	1.25 (0.74–2.10)	1.17 (0.69–1.99)
Predominant type 1 and no type 3 lobules	50	289	0.84 (0.46–1.53)	0.88 (0.48–1.61)
No type 1 lobules or mixed lobule types	129	545	1.0 (REF)	1.0 (REF)
Predominant type 1 and no type 3 lobules	50	289	0.69 (0.47–1.01)	0.77 (0.52–1.13)

*Adjusted for age, year of BBD, and time since benign biopsy.

†Adjusted for above factors and histologic category of BBD.

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) for lobule type and breast cancer risk among participants in the Nurses' Health Study (1988–1994) and Nurses' Health Study II (1991–1995), stratified by histologic category of BBD

	Cases	Controls	OR (95% CI)*
Nonproliferative			
No type 1 lobules or mixed lobule types	31	199	1.0 (REF)
Predominant type 1, no type 3 lobules	16	132	0.73 (0.36–1.50)
Proliferative with no atypia			
No type 1 lobules or mixed lobule types	73	334	1.0 (REF)
Predominant type 1, no type 3 lobules	24	150	0.80 (0.47–1.35)
Atypical hyperplasia			
No type 1 lobules or mixed lobule types	42	61	1.0 (REF)
Predominant type 1, no type 3 lobules	14	39	0.61 (0.28–1.35)
P for interaction between lobule type and BBD category = 0.67			

* Adjusted for age, year of BBD, and time since benign biopsy.

Table 4

Odds ratios (OR) and 95% confidence intervals (CI) for jointly-classified histologic category of BBD/lobule type and breast cancer risk among participants in the Nurses' Health Study (1988–1994) and Nurses' Health Study II (1991–1995)

	Cases	Controls	OR (95% CI)*
Nonproliferative, no type 1 or mixed lobule types	31	199	1.0 (REF)
Nonproliferative, predominant type 1 and no type 3 lobules	16	132	0.80 (0.41–1.54)
Proliferative without atypia, no type 1 or mixed lobule types	73	334	1.43 (0.90–2.28)
Proliferative without atypia, predominant type 1 and no type 3 lobules	24	150	1.09 (0.59–1.99)
Atypical hyperplasia, no type 1 or mixed lobule types	42	61	4.76 (2.67–8.48)
Atypical hyperplasia, predominant type 1 and no type 3 lobules	14	39	2.53 (1.17–5.47)

*Adjusted for age, year of BBD, and time since benign biopsy.