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Radial scars and subsequent breast cancer risk: Results from the Nurses' Health Studies

Sarah A. Aroner[1], **Laura C. Collins**[2], **James L. Connolly**[2], **Graham A. Colditz**[3], **Stuart J. Schnitt**[2], **Bernard A. Rosner**[4,5], **Susan E. Hankinson**[4,6], and **Rulla M. Tamimi**[1,4]

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

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

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

[4]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[5]Department of Biostatistics, Harvard School of Public Health, Boston, MA

[6]Division of Biostatistics and Epidemiology, University of Massachusetts School of Public Health and Health Sciences, Amherst, MA

Abstract

Introduction—Radial scars (RS) are benign proliferative lesions associated with an increased risk of subsequent breast cancer. However, it remains unclear whether RS are an independent risk factor for breast cancer or whether their association with breast cancer is due to their common occurrence with other proliferative lesions known to increase breast cancer risk.

Methods—We performed an updated analysis of the association between RS and subsequent breast cancer risk in a nested case-control study among 460 cases and 1792 controls with benign breast disease (BBD) in the Nurses' Health Studies. Logistic regression was used to estimate associations between RS in BBD biopsy specimens and breast cancer risk, adjusted for matching factors and breast cancer risk factors, including histologic category of concurrent BBD.

Results—In multivariable models prior to adjustment for histologic category of BBD, RS were associated with a two-fold increased risk of breast cancer (odds ratio [OR] = 2.0; 95% confidence interval [95% CI]: 1.4, 2.8). This association was attenuated but still significant after adjustment for BBD histologic category (OR = 1.6; 95% CI: 1.1, 2.3). In models adjusted for BBD histologic category and other covariates, risk appeared greater among women with multiple RS (1 RS, OR = 1.5; 95% CI: 0.9, 2.3; ≥2 RS, OR = 2.7; 95% CI: 1.5, 5.0; p-heterogeneity = 0.12). There were also suggestions of a greater risk associated with RS among women age ≥50 years at biopsy (p-heterogeneity = 0.07) and for estrogen receptor-negative/progesterone receptor-negative (ER−/PR−) tumors compared with other hormone receptor subtypes (p-heterogeneity = 0.19).

Conclusions—RS appear to be an independent histologic risk factor for breast cancer. Larger studies are needed to further evaluate whether risk is increased when multiple RS are present and whether associations vary by age at biopsy or by hormone receptor status of the breast tumor.

Corresponding Author: Sarah A. Aroner, nhsaa@channing.harvard.edu, Phone: (510) 499-9426.

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Keywords

benign breast disease; breast cancer; breast pathology; nested case-control; radial scars

INTRODUCTION

Benign breast disease (BBD) comprises a diverse group of nonmalignant breast abnormalities commonly detected via screening mammography. Although some types of BBD may be premalignant, most are believed to be markers of a generalized increased risk of breast cancer [1]. This risk varies by BBD histologic category; compared with women in the general population, women with nonproliferative disease do not appear to be at elevated risk, whereas those with proliferative disease without atypia (PDWA) are at 1.5–2.0-fold greater risk, and women with proliferative disease with atypia, or atypical hyperplasia (AH), have a 3.5–5.0–fold increased risk [2–4].

Radial scars (RS) are a type of proliferative benign breast lesion characterized by a central fibroelastic core from which ducts and lobules radiate circumferentially [5]. Prior studies have suggested that women with RS are at a two-fold increased risk of breast cancer [6–8], but the nature of the relationship between RS and breast cancer risk remains unclear. Some speculate that RS may be premalignant [9–11] due to their mammographic and histologic resemblance to carcinoma, their frequent association with neoplastic and pre-neoplastic lesions [12–14], and the detection of carcinoma in some RS [14,15,13]. Even if RS are not themselves precancerous, RS may still be independent markers of breast cancer risk that could aid in the identification of women most likely to benefit from risk-reduction strategies. However, as RS are frequently detected in conjunction with other proliferative BBD lesions, the elevated breast cancer risk among women with RS may simply reflect the association of RS with other proliferative lesions, particularly the highest-risk AH lesions.

To investigate whether RS are associated with breast cancer while accounting for the presence of other high-risk BBD lesions, we and two other groups have examined whether the risk associated with RS remains within categories of proliferative BBD (PDWA and AH). In our previous nested case-control study in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) with follow-up from 1976–1992 [6], RS were still associated with a nearly two-fold increased risk after stratifying by BBD category, providing evidence that RS are an independent histologic risk factor for breast cancer; however, the association reached statistical significance only among women with PDWA. In retrospective cohort studies in the Nashville Breast Cohort and Mayo Benign Breast Disease Cohort, no increased risk was observed among women with RS within proliferative BBD categories, suggesting instead that the association between RS and breast cancer is primarily, if not entirely, due to the presence of other proliferative lesions.

To clarify these conflicting results, we conducted an updated and more powerful analysis of the association between RS and breast cancer risk in the NHS/NHSII, with extended follow-up providing approximately 50% more cases than the previous assessment. We also expanded our previous analyses by evaluating whether the association between RS and breast cancer varies by time since or age at biopsy or by tumor hormone receptor subtype.

MATERIALS AND METHODS

Study population

We conducted a nested case-control study among participants with biopsy-confirmed BBD in the NHS and NHS II. The NHS is an ongoing prospective cohort study that began in

1976, when 121,700 female registered nurses between the ages of 30 and 55 years completed a mailed questionnaire. The NHS II is a separate cohort study consisting of 116,609 female registered nurses who were between the ages of 25 and 42 years when the study began in 1989. Participants in both cohorts have been followed via biennial questionnaires that have collected information on lifestyle factors and incident disease. On the 1976, 1978, and 1980 questionnaires, participants were asked if they had ever been diagnosed with fibrocystic or other BBD and whether this diagnosis had required hospitalization; from 1982 onward, the questionnaires have inquired specifically about BBD confirmed by biopsy. 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 so, whether the diagnosis was confirmed by biopsy or aspiration. The follow-up rate for each NHS/NHSII two-year cycle has been greater than 90% of the original cohorts.

Within the subcohort of women who reported a prior diagnosis of BBD confirmed by biopsy, eligible cases were women who reported a first diagnosis of breast cancer between 1976 and the return of the 1998 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; within each NHS cohort, they were matched to up to four breast cancer cases on age at breast cancer diagnosis or index date, year of benign breast biopsy, and time since benign biopsy. Informed consent was obtained from all participants. The study was approved by the Human Subjects Research Committee of Brigham and Women's Hospital, Boston, Massachusetts.

Benign breast biopsy specimens

Eligible cases and controls were contacted for permission to obtain their BBD pathology records and biopsy specimens, and specimens were then obtained from hospital pathology departments when possible. These methods have been described in detail elsewhere [16,17]. Briefly, >70% of the 1310 cases and 6055 controls who were originally identified for the study confirmed the diagnosis and granted permission, and specimens were subsequently obtained for 48% of those who had granted permission (438 cases and 2096 controls). The primary reason given by hospital pathology departments for not sending specimens was that they had been destroyed or were no longer available (36%) [16,17]. Biopsy slides were independently reviewed by one of three study pathologists (SJS, JLC, LCC) who were blinded to the participants' case or control status. The pathologists completed a detailed worksheet with information on the morphologic features of each specimen, including the presence and number of RS. Biopsies were then classified as nonproliferative, PDWA, or AH, according to the criteria of Page *et al.* [18,19], which have been used in previous investigations in this cohort [16,20,2]. All biopsies, including bilateral biopsies, were classified according to the most severe changes present, and specimens with possible or definite AH were jointly reviewed by two pathologists. As RS are considered to be a proliferative lesion, biopsies classified as nonproliferative excluded those with RS.

After excluding participants whose benign biopsy specimens were of poor quality or who had no breast tissue for evaluation, evidence of carcinoma *in situ* or invasive carcinoma, invalid dates of diagnosis, or insufficient information on laterality, 469 cases and 1,842 controls were available for our analyses. An additional 59 participants were excluded for missing data on covariates. Our final population for analysis consisted of 460 cases and 1792 controls.

Statistical analysis

The distribution of breast cancer risk factors was examined according to RS presence among the controls, adjusting for age at benign biopsy when appropriate. Unconditional logistic regression with adjustment for matching factors was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer risk according to RS presence and number. The following covariates, measured in the cycle prior to the breast cancer diagnosis or index date, were considered as potential confounding factors (see Table 2 footnote for variable classifications used): first-degree family history of breast cancer, age at menarche, menopausal status, jointly classified parity and age at first birth, body mass index (BMI) at age 18, and postmenopausal hormone (PMH) use. Because BMI at age 18 appeared to be more strongly related to breast cancer risk than current BMI, we chose to consider adjustment for BMI at age 18 and change in weight since age 18 rather than current BMI. We selected the four covariates producing the greatest change in the OR for inclusion in multivariable models; further adjustment for other covariates did not substantially alter estimates.

In our first set of models, we examined the overall association between RS and breast cancer risk. To assess whether RS were associated with breast cancer risk independent of concurrent proliferative disease, additional adjustment was made for histologic category of BBD in another set of models. We also jointly classified women according to proliferative category and RS presence and stratified by proliferative category to evaluate whether the association between RS and breast cancer risk differed by proliferative category; a likelihood ratio test was used to test for interaction. We examined associations between RS number and breast cancer risk in additional unconditional logistic regression models.

We examined relationships between RS and combined estrogen receptor (ER)/progesterone receptor (PR) status as well as laterality of the subsequent breast cancer (i.e., whether the breast tumor was in the same or opposite breast as BBD) in polytomous logistic regression models. Pathology reports were used as the primary source of information on ER status, PR status, and laterality. Information on receptor status from previously performed tissue microarray analyses (TMA) [21] was used when ER or PR status was not available from pathology reports. Receptor status abstracted from pathology reports has been shown in our cohort to have a high concordance with that obtained from TMA [22]. Women with either bilateral BBD or breast cancer were excluded from the laterality analyses.

To examine whether associations between RS and breast cancer might depend on time since BBD biopsy and age at biopsy, we conducted stratified analyses and tested for interaction in logistic regression models. In stratified analyses, time since BBD biopsy was dichotomized as <10 years and >10 years and age at biopsy as <50 years and >50 years to allow comparison with results from the Nashville and Mayo studies; Wald tests were used to assess whether differences by these factors were statistically significant. We also examined relationships between RS and combined ER/PR status as well as laterality of the breast tumor in polytomous logistic regression models. SAS 9.3 (SAS Institute, Cary, NC) was used for all analyses except tumor subtype analyses, for which STATA 12.1 (StataCorp LP, College Station, TX) was used. All tests were two-sided, with $p < 0.05$ indicating statistical significance.

RESULTS

Among all study participants, the mean age at BBD biopsy was 44.6 years (SD = 10.3 years), the mean time since biopsy was 9.7 years (SD = 7.2 years), and the mean number of slides reviewed was 4.5 (SD = 4.2). Women with RS were on average slightly older at BBD biopsy than women without RS. After adjustment for age at biopsy, the distribution of breast

cancer risk factors was generally similar among women with and without RS, although women with RS had a lower BMI at both BBD biopsy and age 18 as well as slightly higher parity (Table 1).

In multivariable logistic regression models controlling for matching factors and covariates other than BBD histologic category (Table 2), women with RS were at a two-fold higher risk of breast cancer compared with those without RS (OR = 2.0; 95% CI: 1.4, 2.8). After additional adjustment for BBD histologic category, this association remained significant but was moderately attenuated (OR = 1.6; 95% CI: 1.1, 2.3). These associations were essentially unchanged when only invasive breast cancer cases were included (data not shown). The presence of RS was associated with an increased risk of breast cancer both among women with PDWA (OR = 1.8, 95% CI: 1.1, 2.8) and AH (OR = 1.5; 95% CI: 0.8, 2.9). While results were significant only among women with PDWA, there was no evidence that the association differed by BBD proliferative category (p-heterogeneity = 0.38). Women with both RS and AH were at the highest risk compared with women with nonproliferative disease and no RS (OR = 4.8; 95% CI: 2.6, 8.9), although this risk did not differ significantly from that among women with AH and no RS.

Among women with RS, one RS lesion was present in 67.3% of specimens, two lesions were present in 16.7% of specimens, and 3 or more lesions were present in 16.0% of specimens. After adjustment for BBD histologic category and other covariates, women with multiple RS appeared to be at higher risk of breast cancer (RR for ≥2 RS vs. 0 RS = 2.7; 95% CI: 1.5, 5.0) than women with a single RS (RR for 1 vs. 0 RS = 1.5; 95% CI: 0.9, 2.3). However, this difference in risk did not reach significance (p = 0.12).

Multivariable associations between RS and breast cancer were slightly stronger and only significant in the first decade after BBD biopsy (Table 3). After adjustment for BBD histologic category, RS were associated with a 70% increased risk of breast cancer in the first 10 years since BBD biopsy (95% CI: 1.1, 2.7) compared with a 40% increased risk with subsequent follow-up (95% CI: 0.7, 2.6), although this difference by time since biopsy was not significant (p-heterogeneity = 0.57). RS appeared to be associated with breast cancer risk only among women over age 50 at BBD biopsy, with the difference by age approaching significance (p-heterogeneity= 0.07). After adjustment for BBD histologic category, the presence of RS was associated with a three-fold increased risk of breast cancer among women over age 50 years (OR = 3.3; 95% CI: 1.7, 6.1), whereas no increased risk was observed among younger women (OR = 1.1; 95% CI: 0.7, 1.8). These findings were very similar in analyses stratified by menopausal status (data not shown).

The association between RS and breast cancer did not vary significantly by breast cancer hormone receptor subtype in models adjusted for BBD histologic category and other covariates (p-heterogeneity = 0.19), although there was some suggestion of a stronger association for ER−/PR− than either ER+/PR+ or ER+/PR− breast cancer (Table 4). In fact, RS were only significantly associated with risk of ER−/PR− breast cancer, with risk of this subtype nearly three-fold higher for women with RS compared with those without RS (OR=2.8; 95% CI: 1.4, 5.8). RS appeared to be equally associated with ipsilateral and contralateral breast cancer (p-heterogeneity = 0.80).

DISCUSSION

This re-analysis of the association between RS and breast cancer in the NHS/NHSII confirms results from our previous analysis suggesting that RS are an independent histologic risk factor for breast cancer. As in the original analysis, RS were associated with a two-fold increased risk of breast cancer. This association was slightly attenuated after adjustment for

BBD histologic category, suggesting that some of the risk associated with RS reflects their frequent co-occurrence with other proliferative lesions. However, RS remained associated with a nearly two-fold increased risk of breast cancer even after accounting for concurrent proliferative disease. Associations were suggestively stronger for ER−/PR− tumors, among women with multiple RS, and among women older than age 50.

As in our study, the Nashville Breast Cohort and Mayo Benign Breast Disease Cohort studies also observed RS to be associated with a two-fold increased risk of breast cancer, at least in the first 10 years since BBD biopsy. However, the substantial attenuation in risk within BBD proliferative categories in both studies suggests that most, if not all, of this increased risk can be accounted for by concurrent proliferative disease (Table 5). There was some suggestion in both the Nashville and Mayo cohorts as well as in the NHS/NHSII that any independent association between RS and breast cancer may be limited to women with PDWA, but this requires further examination in analyses with greater power to assess associations by BBD category.

We did not find evidence that the risk associated with RS is greater in the first decade after BBD biopsy, as suggested in the Nashville Breast Cohort. However, results from both our study and the Nashville Cohort suggest that the risk associated with RS may be stronger among women older than age 50. In fact, the association between RS and breast cancer, both overall and independent of other BBD lesions, appeared to be limited to women over age 50 in the NHS/NHSII. Although associations by age were based on relatively small numbers in both the NHS/NHSII and Nashville Cohort, an effect of age or menopausal status on the association between RS and breast cancer is supported by the more frequent co-occurrence of RS and breast cancer among women over age 50 reported in several studies [9,14,13].

Differences in methodology and study populations may explain why, unlike in the NHS/NHSII, RS were not found to be a significant independent risk factor for breast cancer in the Nashville and Mayo cohorts. As only our study adjusted for BBD histologic category to assess RS as a potential independent risk factor for breast cancer, it is possible that a modest independent association could have been missed due to small numbers in analyses stratified by BBD category in the Nashville and Mayo studies. In the Mayo study, the use of an external reference group (the Iowa SEER population) that included both women with and without RS may also have led to an underestimate of associations. The weaker associations in the Nashville study may in part reflect the slightly younger population in that cohort compared with the NHS/NHSII, as the association between RS and breast cancer appears to be stronger at older ages. The predominance of biopsies performed in the pre-mammographic era in the Nashville study may also have contributed to the weaker associations in that study, as evidence suggests that the larger RS lesions detected via mammography are more strongly associated with breast cancer risk than those detected primarily as incidental findings in the pre-mammographic era [14,6].

Our results suggest that RS elevate breast cancer risk beyond that of associated proliferative disease, but whether RS might themselves be premalignant or simply a marker for precancerous changes in the breast is uncertain. Some have hypothesized that RS represent an early breast cancer precursor lesion largely based on the finding of carcinoma and precancerous lesions within RS [9,23] and the histologic resemblance of RS to carcinoma, particularly tubular carcinoma [10,11]. This hypothesis is also supported by the detection of similar levels of hyaluronic acid, a component of the extracellular matrix, in RS and tubular carcinoma [24] as well as the observation of abnormal ER expression and chromosomal abnormalities in RS and carcinoma [25]. However, these similarities between RS and carcinoma do not definitively demonstrate that RS are breast cancer precursors. The similar risk associated with ipsilateral and contralateral breast cancer in our study suggests that

instead of being breast cancer precursors, RS are more likely markers for other precancerous changes in the breast [6]. Further work is needed to understand how RS may be related to breast carcinogenesis, although it has been hypothesized that the presence of RS may signal a disruption in normal stromal-epithelial interactions [26], which are believed to play a role in the development of breast and other cancers [27–30]. The similarly increased mRNA expression of stromal vascular factors observed in RS and invasive carcinoma [26] and the loss of fibrocytic stromal cells in both RS and tubular carcinoma [31] support the notion that RS are related to precancerous stromal changes.

Our study is, to our knowledge, the first to examine the association between RS and breast cancer by hormone receptor subtype. The apparent stronger association between RS and ER −/PR− compared with ER+/PR+ or ER+/PR− breast cancer suggests that RS may signal the presence of non-hormonal premalignant changes in the breast. However, this stronger association with receptor-negative subtypes is somewhat puzzling given that previous clinical studies have reported RS to be most frequently found in conjunction with tubular carcinoma [15,32], a breast cancer subtype that is most commonly ER+/PR+ [33,34]. Given this unexpected association with hormone receptor-negative cancers and the small numbers in analyses by receptor subtype, our findings require confirmation in future studies.

Our study has several limitations and strengths. Even with approximately 50% more cases than the previous NHS analysis, power was limited in analyses examining potential effect modifiers and even more so in analyses by ER/PR subtype, as not all participants had information available on hormone receptor subtypes. Additionally, we were only able to obtain BBD biopsy slides for approximately one-third of study participants. However, the success rate did not differ by case-control status and women appeared to be missing completely at random, as those with and without specimens were similar with respect to their distribution of breast cancer risk factors, including BMI, parity, and PMH. Strengths of our study are its prospective design, the confirmation of breast cancer cases via medical record review, the centralized pathology review of BBD specimens, and the detailed collection of information on potential confounders.

In conclusion, our results suggest that RS are associated with risk of subsequent breast cancer independent of simultaneous proliferative disease. As RS may further elevate risk among women with other high-risk lesions, our findings have potentially important clinical implications. However, future studies with larger numbers of cases are needed to confirm our main results and to further evaluate whether risk is influenced by the presence of multiple RS, age at biopsy, and hormone receptor status of the breast tumor.

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REFERENCES

1. Page DL, Dupont WD. Benign breast disease: indicators of increased breast cancer risk. Cancer Detect Prev. 1992; 16(2):93–97. [PubMed: 1600526]

2. 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):941–944. [PubMed: 1734106]
3. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, Vierkant RA, Maloney SD, Pankratz VS, Hillman DW, Suman VJ, Johnson J, Blake C, Tlsty T, Vachon CM, Melton LJ 3rd, Visscher DW. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005; 353(3): 229–237. [PubMed: 16034008]
4. Dupont WD, Parl FF, Hartmann WH, Brinton LA, Winfield AC, Worrell JA, Schuyler PA, Plummer WD. Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer. 1993; 71(4):1258–1265. [PubMed: 8435803]
5. Wellings SR, Alpers CE. Subgross pathologic features and incidence of radial scars in the breast. Human Pathology. 1984; 15(5):475–479. [PubMed: 6724567]
6. Jacobs TW, Byrne C, Colditz G, Connolly JL, Schnitt SJ. Radial scars in benign breast-biopsy specimens and the risk of breast cancer. New England Journal of Medicine. 1999; 340(6):430–436. [PubMed: 9971867]
7. Sanders ME, Page DL, Simpson JF, Schuyler PA, Dale Plummer W, Dupont WD. Interdependence of radial scar and proliferative disease with respect to invasive breast carcinoma risk in patients with benign breast biopsies. Cancer. 2006; 106(7):1453–1461. [doi]. [PubMed: 16502407]
8. Berg JC, Visscher DW, Vierkant RA, Pankratz VS, Maloney SD, Lewis JT, Frost MH, Ghosh K, Degnim AC, Brandt KR, Vachon CM, Reynolds CA, Hartmann LC. Breast cancer risk in women with radial scars in benign breast biopsies. Breast Cancer Research and Treatment. 2008; 108(2): 167–174. [PubMed: 18297395]
9. Manfrin E, Remo A, Falsirollo F, Reghellin D, Bonetti F. Risk of neoplastic transformation in asymptomatic radial scar. Analysis of 117 cases. Breast Cancer Research and Treatment. 2008; 107(3):371–377. [PubMed: 17457669]
10. Linell F, Ljungberg O, Andersson I. Breast carcinoma. Aspects of early stages, progression and related problems. Acta Pathol Microbiol Scand Suppl. 1980; (272):1–233. [PubMed: 6254324]
11. Fisher ER, Palekar AS, Kotwal N, Lipana N. A nonencapsulated sclerosing lesion of the breast. Am J Clin Pathol. 1979; 71(3):240–246. [PubMed: 219682]
12. Vega A, Mosquera J, Delgado A, Sogo C, Ortega E, Garijo F, Alvarez A. Proliferative changes in nonpalpable breast lesions detected by mammography. Radiologia. 2000; 42(5):299–304.
13. Douglas-Jones AG, Pace DP. Pathology of R4 spiculated lesions in the breast screening programme. Histopathology. 1997; 30(3):214–220. [PubMed: 9088949]
14. Sloane JP, Mayers MM. Carcinoma and atypical hyperplasia in radial scars and complex sclerosing lesions: Importance of lesion size and patient age. Histopathology. 1993; 23(3):225–231. [PubMed: 8225240]
15. Frouge C, Tristant H, Guinebretiere JM, Meunier M, Contesso G, Di Paola R, Blery M. Mammographic lesions suggestive of radial scars: microscopic findings in 40 cases. Radiology. 1995; 195(3):623–625. [PubMed: 7753984]
16. 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):180–187. [PubMed: 17154175]
17. 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):1240–1247. [PubMed: 16902983]
18. Schnitt, SJ.; Connolly, JL. Pathology of benign breast disorders. In: Harris, JRLME.; Morrow, M.; Osborne, CK., editors. Diseases of the breast. 3rd edn.. Philadelphia: Lipincott Williams & Wilkins; 2004. p. 69-86.
19. 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):2698–2708. [PubMed: 2986821]
20. Marshall LM, Hunter DJ, Connolly JL, Schnitt SJ, Byrne C, London SJ, Colditz GA. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev. 1997; 6(5):297–301. [PubMed: 9149887]

21. Tamimi RM, Baer HJ, Marotti J, Galan M, Galaburda L, Fu Y, Deitz AC, Connolly JL, Schnitt SJ, Colditz GA, Collins LC. Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. Breast Cancer Res. 2008; 10(4):R67. [PubMed: 18681955]
22. Collins LC, Marotti JD, Baer HJ, Tamimi RM. Comparison of estrogen receptor results from pathology reports with results from central laboratory testing. J Natl Cancer Inst. 2008; 100(3): 218–221. [PubMed: 18230800]
23. Mokbel K, Price RK, Carpenter R. Radial scars and breast cancer. N Engl J Med. 1999; 341(3): 210. [PubMed: 10409044]
24. de la Torre M, Wells AF, Bergh J, Lindgren A. Localization of hyaluronan in normal breast tissue, radial scar, and tubular breast carcinoma. Hum Pathol. 1993; 24(12):1294–1297. [PubMed: 8276376]
25. Iqbal M, Shoker BS, Foster CS, Jarvis C, Sibson DR, Davies MPA. Molecular and genetic abnormalities in radial scar. Human Pathology. 2002; 33(7):715–722. [PubMed: 12196923]
26. Jacobs TW, Schnitt SJ, Tan X, Brown LF. Radial scars of the breast and breast carcinomas have similar alterations in expression of factors involved in vascular stroma formation. Human Pathology. 2002; 33(1):29–38. [PubMed: 11823971]
27. Bissell MJ, Weaver VM, Lelievre SA, Wang F, Petersen OW, Schmeichel KL. Tissue structure, nuclear organization, and gene expression in normal and malignant breast. Cancer Res. 1999; 59(7 Suppl):1757–1763s. discussion 1763s–1764s. [PubMed: 10197593]
28. Hansen RK, Bissell MJ. Tissue architecture and breast cancer: the role of extracellular matrix and steroid hormones. Endocr Relat Cancer. 2000; 7(2):95–113. [PubMed: 10903527]
29. Wang F, Weaver VM, Petersen OW, Larabell CA, Dedhar S, Briand P, Lupu R, Bissell MJ. Reciprocal interactions between beta1-integrin and epidermal growth factor receptor in three-dimensional basement membrane breast cultures: a different perspective in epithelial biology. Proc Natl Acad Sci U S A. 1998; 95(25):14821–14826. [PubMed: 9843973]
30. Ronnov-Jessen L, Petersen OW, Bissell MJ. Cellular changes involved in conversion of normal to malignant breast: importance of the stromal reaction. Physiol Rev. 1996; 76(1):69–125. [PubMed: 8592733]
31. Ramaswamy A, Moll R, Barth PJ. CD34+ fibrocytes in tubular carcinomas and radial scars of the breast. Virchows Arch. 2003; 443(4):536–540. [PubMed: 12898244]
32. Vega A, Garijo F. Radial scar and tubular carcinoma. Mammographic and sonographic findings. Acta Radiol. 1993; 34(1):43–47. [PubMed: 8427748]
33. Cabral AH, Recine M, Paramo JC, McPhee MM, Poppiti R, Mesko TW. Tubular carcinoma of the breast: an institutional experience and review of the literature. Breast J. 2003; 9(4):298–301. [PubMed: 12846864]
34. Sullivan T, Raad RA, Goldberg S, Assaad SI, Gadd M, Smith BL, Powell SN, Taghian AG. Tubular carcinoma of the breast: a retrospective analysis and review of the literature. Breast Cancer Res Treat. 2005; 93(3):199–205. [PubMed: 16142444]

Table 1

Characteristics by radial scar status among controls with benign breast disease in the Nurses' Health Study (1976–1998) and Nurses' Health Study II (1991–1995)*

	Radial Scars	No Radial Scars	*P*
No. of controls (%)	112 (6.3)	1680 (93.8)	
Means (SEs)			
Age at BBD biopsy, years	47.3 (0.7)	44.4 (0.3)	0.004**
Year of BBD biopsy	1980 (0.7)	1980 (0.2)	0.48**
Body mass index, kg/m^2†	23.7 (1.3)	25.0 (1.8)	0.03
Body mass index at age 18, kg/m^2†	20.1 (0.7)	21.0 (1.1)	0.003
Age at menarche, years†	12.5(0.5)	12.6 (0.6)	0.17
Weight change since age 18, kg†	9.4 (3.4)	10.8 (4.2)	0.51
Age at first birth, years (parous only)†	25.0 (1.3)	24.9 (1.4)	0.49
Alcogol intake, g/day†	4.1 (2.8)	4.0 (3.2)	0.97
Parity (parous only)†	3.3 (0.6)	3.0 (0.5)	0.01
Percentages			
Premenopausal†	31.0	34.0	0.77
Parous†	89.5	91.9	0.91
First degree family history of breast cancer†	20.3	17.5	0.53
Ever postmenopausal hormone use†	42.4	38.9	0.60
Histologic category of BBD†			<0.0001
Nonproliferative‡	-	38.4	
Proliferative without atypia	77.9	52.0	
Atypical hyperplasia	22.1	9.6	

BBD indicates benign breast disease; SE indicates standard error.

*Unless otherwise specified, all variables correspond to the time period immediately prior to the index date.

**p values were obtained from analysis of variance models.

†Means and percentages were standardized to the controls at the time of benign biopsy, in 5-years categories. Age-adjusted p values were obtained from linear regression models for means and logistic regression models for percentages.

‡Radial scars were classified as proliferative BBD; therefore, no controls with radial scars were considered to have non-proliferative BBD

Table 2

ORs and 95% CIs for radial scars and breast cancer risk among participants with benign breast disease in the Nurses' Health Study (1976–1998) and Nurses' Health Study II (1991–1995)

	Cases	Controls	OR (95%CI)*	OR (95% CI)†
Radial scar status				
No radial scars	405	1680	1.0 (reference)	1.0 (reference)
Radial scars	55	112	2.2 (1.5, 3.0)	2.0 (1.4, 2.8)
Radial scar status, adjusted for BBD histologic category				
No radial scars	405	1680	1.0 (reference)	1.0 (reference)
Radial scars	55	112	1.7 (1.2, 2.4)	1.6 (1.1, 2.3)
Jointly classified BBD/radial scar histologic category				
Nonproliferative	108	647	1.0 (reference)	1.0 (reference)
Proliferative without atypia				
No radial scars	200	873	1.4 (1.1, 1.8)	1.4 (1.0, 1.8)
Radial scars	33	84	2.6 (1.6, 4.1)	2.4 (1.5, 3.9)
Atypical hyperplasia				
No radial scars	97	160	3.9 (2.8, 5.5)	3.8 (2.7, 5.3)
Radial scars	22	28	5.3 (2.9, 9.8)	4.8 (2.6, 8.9)
Radial scar status, stratified by BBD histologic category				
Proliferative without atypia				
No radial scars	200	873	1.0 (reference)	1.0 (reference)
Radial scars	33	84	1.8 (1.1, 2.7)	1.8 (1.1, 2.8)
Atypical hyperplasia				
No radial scars	97	160	1.0 (reference)	1.0 (reference)
Radial scars	22	28	1.5 (0.8, 2.7)	1.5 (0.8, 2.6)

*Adjusted for age at breast cancer diagnosis/index date (<45 years, 45 to 49 years, 50 to 54 years, 55 to 59 years, ≥60 years), year of benign breast disease (BBD) diagnosis (before 1970, 1970 to 1979, 1980 to 1989, 1990 and later), and time since BBD biopsy (years from BBD diagnosis to breast cancer diagnosis/index date, continuous)

†Adjusted for the above-mentioned factors and boby mass index at age 18 (<21, 21 to 22.9, 23 to 24.9, ≥25 kg/m^2), weight change since age 18 (<5 kg, 5 to <20 kg, ≥20 kg), family history of breast cancer (yes/no), age at menarche (<12 years, 12 years, 13 years, ≥14 years), and jointly classified parity/age at first birth (nulliparous, 1 to 2 children and <25 years, 1 to 2 children and 25 to 29 years, 1 to 2 children and ≥30 years, ≥3 children and <25 years, ≥3 children and ≥25 years)

Table 3

ORs and 95% CIs for radial scars and breast cancer risk by time since BBD biopsy and age at BBD biopsy

	Cases	Controls	OR (95% CI)†	Cases	Controls	OR (95% CI)†	*p* - het*
	<10 years since BBD biopsy			**≥10 years since BBD biopsy**			
Radial scar status							
No radial scars	225	996	1.0 (reference)	180	684	1.0 (reference)	
Radial scars	36	74	2.1 (1.4, 3.3)	19	38	1.7 (0.9, 3.2)	0.46
Radial scar status, adjusted for BBD histologic category							
No radial scars	225	996	1.0 (reference)	180	684	1.0 (reference)	
Radial scars	36	74	1.7 (1.1, 2.7)	19	38	1.4 (0.7, 2.6)	0.57
	Age <50 years at BBD biopsy			**Age ≥50 years at BBD biopsy**			
Radial scar status							
No radial scars	299	1152	1.0 (reference)	106	528	1.0 (reference)	
Radial scars	32	74	1.5 (0.9, 2.3)	23	38	3.8 (2.1, 6.9)	0.15
Radial scar status, adjusted for BBD histologic category							
No radial scars	299	1152	1.0 (reference)	106	528	1.0 (reference)	
Radial scars	32	74	1.1 (0.7, 1.8)	23	38	3.3 (1.7, 6.1)	0.07

†Adjusted for matching factors (age, year of BBD diagnosis, time since BBD biopsy) and body mass index at age 18,weight change since age 18 family history of breast cancer, age at menarche, and jointly classified parity/age at first birth

*p for heterogeneity of the association between radial scars and breast cancer (adjusted for matching factors and other covariates), by time since BBD biopsy (<10 years vs. ≥10 years) and age at BBD biopsy (<50 years vs. ≥50 years)

Table 4

ORs and 95% CIs for radial scars and breast cancer combined ER/PR status among participants with BBD in the Nurses' Health Study (1976–1998) and Nurses' Health Study II (1991–1995)

	No radial scars	Radial scars	*P* for heterogeneity, by ER/PR status
No. of ER+/PR+ cases	185	21	
No. of ER+/PR− cases	33	5	
No. of ER−/PR− cases	57	12	
No. of controls	1680	112	
Multivariate OR (95% CI) *			
ER+/PR+ cases vs. controls	1.0 (ref)	1.7 (1.0, 2.8)	
ER+/PR− cases vs. controls	1.0 (ref)	2.1 (0.8, 5.7)	0.30
ER−/PR− cases vs. controls	1.0 (ref)	3.2 (1.6, 6.3)	
Multivariate OR (95% CI)*, additionally adjusted for BBD category			
ER+/PR+ cases vs. controls	1.0 (ref)	1.3 (0.8, 2.2)	
ER+/PR− cases vs controls	1.0 (ref)	1.5 (0.5, 4.2)	0.19
ER−/PR− cases vs. controls	1.0 (ref)	2.8 (1.4, 5.8)	

OR indicates odds ratio; 95% CI, 95% confidence interval; ER, estrogen receptor; PR, progesterone receptor; BBD, benign breast disease

*Calculated using polytomous logistic regression adjusted for matching factors and body mass index at age 18, weight change since age 18, family history of breast cancer, age at menarche, and jointly classified parity/age at first birth

Table 5

Relative risks (RRs) and 95% CIs from studies examining the association between radial scars and breast cancer risk*

	Nurses' Health Study, updated analysis	Nashville Breast Cohort†	Mayo Benign Breast Disease Cohort‡
All women			
Total no	2252**	9556	9262
No. with RS	167	880	439
No. of breast cancer cases	460	197	52§
Multivariate RR (95% CI)	**2.0 (1.4, 2.8)**	**1.8 (1.2, 2.6)**	**2.0 (1.5, 2.6)**
Proliferative disease without atypia			
Total no	1190	3404	2693
No. with RS	117	697	379
No. of breast cancer cases	233	91	43
Multivariate RR (95% CI)	**1.8 (1.1, 2.8)**	**1.3 (0.7, 2.3)**	**1.2 (0.9, 1.7)**
Atypical hyperplasia			
Total no.	307	365	325
No. with RS	50	110	60
No. of breast cancer cases	119	27	9
Multivariate RR (95% CI)	**1.5 (0.8, 2.9)**	**1.1 (0.5, 2.8)**	**0.7 (0.3, 1.5)**

*RRs in the Nashville and Mayo studies were presented using non-proliferative disease with no RS and the lowa SEER registry as the reference categories, respectively. We used these RRs to calculate RRs within each proliferative category (PDWA and AH), using women without RS as the reference. All associations are for invasive + *in situ* breast cancer.

**Cases and controls

†First 10 years of follow-up (estimates across total follow-up time not presented in the Nashville study); adjusted for age at biopsy, year of biopsy, parity, age at first birth, and age at menopause

‡Adjusted for age and calender period

§RRs were calculated by standardized incidence ratios, which used only cases with RS in the Mayo cohort