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REVIEW

# Breast cancer risk associated with benign breast disease: systematic review and meta-analysis

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**Abstract** Benign breast disease (BBD) is a broad category of diagnoses reported to convey a variable degree of increased risk of developing breast cancer. A meta-analysis of the existing literature was performed to quantify the risk estimate associated with BBD. Pubmed, Google Scholar, and EMBASE databases were searched in January 2011. English retrospective and prospective observational studies published from 1972 to 2010 evaluating BBD and the risk of breast cancer were included with data acquisition reported from 1930 to 2007. Eligibility was performed independently following a standardized protocol for full-text publication review by a single reviewer and reviewed by a second author. Of the 3,409 articles retrieved from the literature search, 32 studies met the selection criteria. Reported risk estimates, including relative risk, odds ratio, standardized incidence ratios, rate ratio, hazards ratio, and incidence rate ratio, were the primary outcomes extracted. The most commonly reported pathologies were decided prior to extraction and organized into the following categories for analysis of the extracted risk estimate: non-proliferative disease (NPD), proliferative disease without atypia, benign breast disease not otherwise specified (BBD), and atypical hyperplasia not otherwise specified (AHNOS). The mean age at benign breast biopsy was 46.1 years and the mean age of developing breast cancer was 55.9 years. The mean follow-up length was 12.8 years (range 3.3–20.6). The summary risk estimate of developing breast cancer for NPD was 1.17 ($N = 8$; 95 % CI 0.94–1.47). Proliferative disease without atypia was associated with significantly increased risk of future breast cancer, summary relative risk 1.76 ($N = 15$; 95 % CI 1.58–1.95). The summary risk estimate for AHNOS was 3.93 ($N = 13$; 95 % CI 3.24–4.76). This meta-analysis demonstrates that proliferative benign breast disease with or without atypia is associated with a significant increase in risk of developing breast cancer. These data support management strategies for women with benign breast disease such as additional screening methods or chemoprevention.

**Keywords** Benign breast disease · Breast cancer · Atypia · Meta-analysis

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## Introduction

Benign breast disease (BBD) is a broad category of pathologic diagnoses including, but not limited to fibroadenomas, cysts, fibrocystic disease, papillomas, and ductal

epithelial proliferations with or without atypia. Studies have demonstrated a 4–5-fold increased risk of developing breast cancer in individuals demonstrating BBD with atypia and a 1.5–2-fold increased risk of developing breast cancer in individuals with BBD without atypia [1]. The underlying cause of BBD remains unknown, though the pathway from normal terminal ductal lobule to premalignant breast lesions, noninvasive, and invasive cancer has been well described morphologically [2]. The histologic evolution of ductal breast cancer was initially introduced by Wellings and Jensen. The modified Wellings Jensen model of breast cancer development describes how hyperplastic breast epithelial cells slowly enlarge the terminal duct lobular units; forming hyperplastic enlarged lobular units that may then lead to microcysts or development of usual ductal hyperplasia or atypical ductal hyperplasia (ADH). ADH may develop into ductal carcinoma in situ and then may develop eventually into invasive breast malignancy [3]. Genetic predisposition and environmental factors, such as diet, alcohol, and physical activity, may modify the development of benign lesions, though mechanisms are poorly understood [4–10].

Challenges in studying the epidemiology of BBD include the lack of widespread use of a standardized histologic classification system for BBD and the lack of true prevalence estimates in the general population. The cumulative incidence of biopsy-proven BBD is approximately 10–20 %, whereas autopsy studies have demonstrated much higher prevalence, at approximately 50 % [11]. Whether some of the conditions of BBD (such as proliferative disease with atypia) are direct precursors to premalignant and invasive malignancy, as postulated by the modified Wellings Jensen model, versus purely risk indicators, remains unclear [12]. Given the variable increased risk of breast cancer in women with BBD reported by multiple studies, a formal meta-analysis of the existing literature was performed to better quantify the risk estimate associated with BBD including both proliferative and non-proliferative conditions.

## Methods

### Protocol and registration

No standard protocol or registration was utilized; rather, we followed established methods and approaches to searching, defining eligibility, and analysis.

### Eligibility criteria

Published observational studies including retrospective and prospective case–control and cohort studies evaluating benign breast disease and the risk of developing breast cancer were included in this study. There were no publication date restrictions. Studies published in English from multiple continents were included in this study. The primary outcome evaluated was the risk estimate of developing breast cancer in individuals with a history of confirmed benign breast disease. The risk estimates extracted from the studies included relative risk, odds ratio, standardized incidence ratios, rate ratio, hazards ratio, and incidence rate ratio.

### Information sources and search

Studies were identified by searching MEDLINE (1966-present) via Pubmed, Google Scholar (1972-present), and EMBASE (1980-present). The date of the most recent search was January 2nd, 2011. Full articles available in English that evaluated the risk of breast cancer in individuals with benign breast disease were included in the meta-analysis.

The Pubmed database search was conducted using the search terms: benign breast disease and breast cancer. This yielded 320 search items. After review of these search items, 62 potential primary subject articles were identified. The EMBASE database search was conducted utilizing the search terms: benign breast disease and breast cancer, benign breast disease and breast cancer risk, benign proliferative breast disease and breast cancer, and benign proliferative breast disease, and breast cancer risk which yielded 1069, 185, 107, and 25 items, respectively. After review of these search items, 14 potential primary subject articles were identified. The original Google Scholar Search utilizing the terms: benign breast disease and breast cancer that yielded approximately 953,000 search items. The first 1,000 items of these were reviewed and this yielded 33 potential primary subject articles. Utilizing the same search engine, benign breast disease and breast cancer, the modified Google Scholar Search with the limitation of "Exact Phrase" yielded 541 search items and the additional modified Google Scholar Search with the limitation of "All in Title" yielded 155 search items. Utilizing the search engine: benign proliferative breast disease AND breast cancer, a modified Google Scholar Search with the limitation of "All in Title" yielded seven potential items. After these items from the modified Google Scholar Search were reviewed, an additional 19 potential primary subject articles were identified. Thus in total, the Google Search identified 52 potential primary subject articles. Throughout the three database searches, there were 128 potential primary subject articles identified. Twenty-three additional related articles were identified during data extraction from the bibliographies of the articles obtained from the primary database search, five of which were potential primary subject articles. During data extraction, 55 of these primary

subject articles were found to be relevant to the focus of the meta-analysis. Fifteen of these 55 primary subject articles dealt specifically with one type of benign breast condition. After eliminating duplicate reports from a study patient population and eliminating studies that did not report a risk estimate with confidence intervals, there were 32 studies [13–44] that were used in quantitative synthesis of this meta-analysis and 23 studies [13–15, 17–23, 26–29, 31, 33–36, 38, 40, 42, 44] that were used specifically in quantitative synthesis of the categories: non-proliferative disease (NPD), proliferative without atypia, benign breast disease not otherwise specified (BBD), and atypical hyperplasia not otherwise specified (AHNOS). See Appendix A.

### Study selection

Eligibility assessment was performed independently in a standardized manner utilizing title, abstract, and full-text publication by a single reviewer and then reviewed by a second author as detailed in Fig. S1.

### Data collection process

We developed a data extraction excel sheet, pilot tested it on approximately ten included studies, and refined it accordingly. One review author performed data extraction and a second author reviewed the extracted data. Disagreements were resolved by discussion between the authors.

### Data items

Information was extracted from each included trial on (1) trial participants' characteristics (publication date, acquisition date range, reported patient age, study location, reported follow-up, review method), (2) benign breast disease assessment, and (3) risk estimate for each subclassification of benign breast lesions and number of adjusted factors.

### Summary measures

Risk estimates including relative risk, odds ratio, standardized incidence ratios, rate ratio, hazards ratio, and incidence rate ratio were the primary measures of breast cancer risk in patients with benign breast disease.

### Synthesis of results

Random effects meta-analysis was used to allow for the heterogeneity of results across studies [45]. Data were processed in SAS and the analyses were performed using R-package "meta". Since most studies reported relative risks (RR) or odds ratios (OR) and their associated 95 percent confidence intervals (CI), these were chosen as summary statistics for each study. The standard error of log (RR or OR) using the 95 percent CI was derived with the expression: [log (upper limit) − log (lower limit)]/$2 \times 1.96$, assuming that the logarithms of the risk estimates have a normal distribution. These standard errors were used as weights for summary effect estimates in the meta-analysis. To examine the homogeneity of the effect size across studies, we used Cochrane Q statistic, which is distributed as Chi square with degrees of freedom (number of study-1) under the null homogeneity hypothesis [45]. Publication bias was visually examined by Funnel plot and formally tested by rank correlation methods [46]. These analyses were performed separately for non-proliferative disease, proliferative disease without atypia, benign breast disease not otherwise specified, atypical hyperplasia not otherwise specified, atypical ductal hyperplasia, atypical lobular hyperplasia, adenosis, cysts not otherwise specified, fibroadenoma, and papilloma not otherwise specified.

### Risk of bias

The possibility of publication bias was assessed by evaluating the rank correlation test of funnel plot asymmetry in regards to the analysis of non-proliferative disease, proliferative disease without atypia, benign breast disease not otherwise specified, and atypical hyperplasia not otherwise specified.

### Additional analyses

The reported time from diagnosis of benign breast disease to development of breast cancer, the age at first biopsy for BBD, and the age at breast cancer diagnosis were also analyzed when reported to explore their potential as modifiers of risk estimates [13, 15, 16, 27, 30, 31, 33, 36–38, 40, 42, 47, 48].

## Results

### Study selection

Initial literature search yielded 3,409 potential articles with a final number of 34 studies included for quantitative synthesis of this meta-analysis after exclusion criteria were applied (Fig. S1).

### Study characteristics

Published retrospective and prospective case–control studies from 1972 to 2010 evaluating benign breast disease

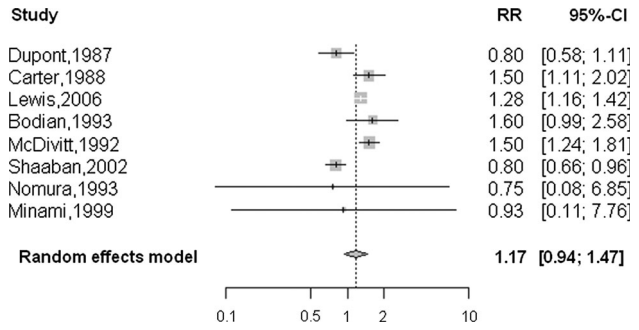


**Fig. 1** Non-proliferative

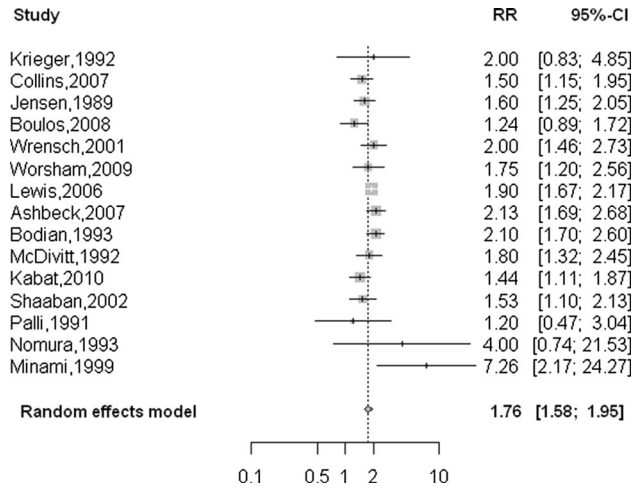


**Fig. 2** Proliferative disease without atypia

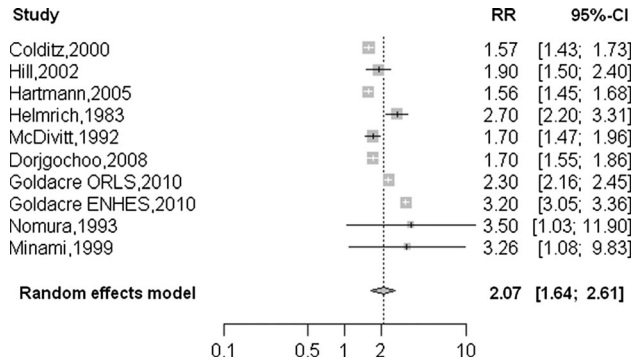


**Fig. 3** Benign breast disease not otherwise specified (BBD)

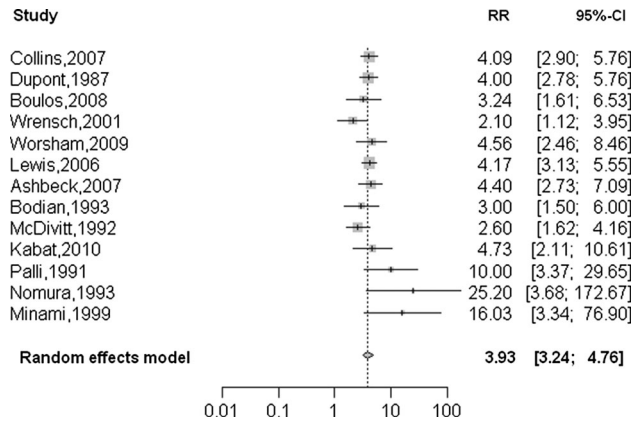


**Fig. 4** Atypical Hyperplasia not otherwise specified (AHNOS)

and the risk of breast cancer were included in this study with patient data acquisition reported from 1930 to 2007 (Table S1). The mean reported age at benign breast biopsy was 46.6 years (32.7–57.3) and the mean age of developing breast cancer was 55.9 years (49–63.2) (Table S2). The mean follow-up length was 12.8 years (range 3.3–20.6) (Table S1).

## Results of individual studies

Twenty-four of these studies were used specifically for analysis of the categories: non-proliferative disease, proliferative disease without atypia, benign breast disease not otherwise specified, and atypical hyperplasia not otherwise specified. Consistent with the variability of published results, the reported risk estimates for developing breast cancer in the 8 studies evaluating non-proliferative disease ranged from 0.75 to 1.60 (Fig. 1). Risk estimate reported in the 15 studies evaluating proliferative disease without atypia ranged from 1.20 to 7.26 (Fig. 2). Risk estimates reported in the 10 studies evaluating benign breast disease not otherwise specified ranged from 1.70 to 3.50 (Fig. 3). Reported risk estimates in the 13 studies evaluating atypical hyperplasia not otherwise specified ranged from 2.10 to 25.20 (Fig. 4).

## Syntheses of results

The summary risk estimate of developing breast cancer following a biopsy showing non-proliferative disease was 1.17 (95 % CI 0.94–1.47), based on 8 studies (Fig. 1). The summary risk estimate for breast cancer following proliferative disease without atypia was 1.76 (95 % CI 1.58–1.95), based on 15 studies (Fig. 2). The summary risk estimate for benign breast disease not otherwise specified was 2.07 (95 % CI 1.64–2.61), based on 10 studies with significant heterogeneity ($I^2 = 97.8$ %; df = 9, $p < 0.0001$) (Fig. 3). The summary risk estimate for atypical hyperplasia not otherwise specified was 3.93 (95 % CI 3.24–4.76), based on 13 studies (Fig. 4). There was significant heterogeneity in the studies evaluating non-proliferative disease ($I^2 = 79.7$ %; df = 7, $p = <0.0001$) and benign breast disease not otherwise specified ($I^2 = 97.8$ %; df = 9, $p < 0.0001$). No significant heterogeneity was identified in the studies evaluating proliferative disease without atypia ($I^2 = 40.1$ %, df = 14,

$p = 0.0542$) and atypical hyperplasia not otherwise specified ($I^2 = 33.2$ %; df = 12, $p = 0.1166$).

Risk of bias

Publication bias was observed in non-proliferative disease (Fig. S2), benign breast disease not otherwise specified (Fig. S3), and minimal in proliferative disease without atypia (Fig. S4). Publication bias was not observed in atypical hyperplasia not otherwise specified (Fig. S5).

Additional analyses

*Histologic characteristics*

Analysis of the 7 studies reporting adenosis demonstrated a summary risk estimate of 2.00 (95 % CI 1.46–2.74) (Fig. S6). The 6 studies reporting atypical ductal hyperplasia demonstrated a summary risk estimate of 3.28 (95 % CI 2.54–4.23) (Fig. S7). The 6 studies reporting atypical lobular hyperplasia demonstrated a summary risk estimate of 3.92 (95 % CI 2.81–5.47) (Fig. S8). The 9 studies that reported cysts not otherwise specified demonstrated a summary risk estimate of 1.55 (95 % CI 1.26–1.90) (Fig. S9). The 11 studies reporting fibroadenoma demonstrated a summary risk estimate of 1.41 (95 % CI 1.11–1.80) (Fig. S10). The 8 studies reporting papilloma not otherwise specified demonstrated a summary risk estimate of 2.06 (95 % CI 1.38–3.07) (Fig. S11). Significant heterogeneity existed for all of these studies except for atypical ductal hyperplasia and atypical lobular hyperplasia (Table S3).

*Time from biopsy to diagnosis of breast cancer*

Several of the studies also reported the average time to developing breast cancer after the initial biopsy of BBD, the age at the first biopsy, and the age at breast cancer diagnosis, which are clinically relevant (Table S2). The mean duration from initial diagnosis of benign breast disease to diagnosis of breast cancer was 9.4 years, based on the 10 studies that reported the average duration.

## Discussion

This is the first meta-analysis, to the best of our knowledge, performed on multiple published studies evaluating the association of biopsy-proven benign breast disease with risk of developing breast cancer. We found that proliferative benign breast disease with or without atypia is associated with an increased risk of developing breast cancer with the highest measured relative risk of nearly 4-fold for atypical hyperplasia not otherwise specified. There was no heterogeneity among study results for proliferative benign breast disease or atypical hyperplasia not otherwise specified.

One limitation of this meta-analysis includes the lack of uniform reporting on specific BBD pathologies when comparing studies from multiple countries. We addressed this, in part, by using four main histologic categories. Given the lack of uniform reporting on specific BBD pathologies, there may be overlap between the four main and six additional histological types. Also, follow-up of patients included in these studies did not always account for patient relocation, allowing the possibility of additional breast cancers diagnosed in individuals not included in the follow-up studies. The reported review method and number of adjusted factors in the reported risk estimate were also extracted. Given the large number of studies included in this meta-analysis and the variable number of adjusted factors and reported review method, additional statistical analysis was not performed and is a potential limitation of this meta-analysis.

Uniform classification and reporting of benign breast disease is needed to better delineate the relationship of specific benign breast disease pathologies and increased risk of breast cancer [11]. Furthermore, uniform measures of reporting risk estimates are needed to improve the clarity of implications for clinicians. For this purpose, Elmore and Gigerenzer recommend reporting results in terms of absolute risk as opposed to relative risk [12].

These summary estimates of breast cancer risk following benign breast biopsy have the potential to help improve clinician knowledge and patient education and guide screening recommendations. Women with benign proliferative breast disease should more closely adhere to the currently recommended American Cancer Society (ACS) guidelines for breast cancer screening which support annual screening beginning at 40 years old. It remains unclear if the increased risk associated with proliferative benign breast disease is significant in magnitude to justify additional screening approaches, such as breast MRI, which is recommended by the ACS for women with a >20 % calculated lifetime risk of breast cancer. The Gail Model is a commonly used clinical tool to calculate an individual woman's risk of developing breast cancer over the next 5 years and by the age of 90. Both the number of prior breast biopsies and the presence of atypia on biopsy are incorporated in the Gail model. However, Pankratz et al. showed that the Gail model significantly underestimates the risk of breast cancer in women with atypia and directed clinicians to use caution when using the Gail model to counsel these women [49]. Recognizing the increased risk of breast cancer in patients with benign proliferative breast disease may help to improve current risk assessment models used for determining screening recommendations [50].

Further research is also necessary to determine the potential beneficial effects of chemoprevention strategies such as anti-estrogen medications. Khan et al. demonstrated that individuals with BBD and breast cancer were more likely to have estrogen receptor-positive epithelium than those patients with BBD without cancer and thus have the potential to be sensitive to anti-estrogens such as tamoxifen that block estrogen receptor signaling [51]. Data supporting this hypothesis come from the small subset of women with atypical hyperplasia from the National Surgical Adjuvant Breast Project P-1 trial, who had an 86 % reduction in breast cancer risk with the use of tamoxifen [52]. Tan-Chiu et al. in 2003 demonstrated that tamoxifen treatment also reduced the risk of benign breast disease by 28 % (RR = 0.72, 95 % CI 0.65–0.79) and reduced the risk of biopsy by 29 % reduction (RR = 0.71, 95 % CI 0.66–0.77). Additionally, in this study that examined the medical records of the 13,203 women with follow-up participating in the NSABP Breast Cancer Prevention Trial, Tan-Chiu et al. also found that tamoxifen therapy resulted in statistically significant reductions in the risk of adenosis (RR = 0.59, 95 %CI 0.47–0.73), cysts (RR = 0.66, 95 % CI 0.58–0.75), duct ectasia (RR = 0.72, 95 % CI 0.53–0.97), fibrocystic disease (RR = 0.67, 95 % CI 0.58–0.77), hyperplasia (RR = 0.60, 95 % CI 0.41–0.62), metaplasia (RR = 0.51, 95 % CI 0.41–0.62), fibroadenoma (RR = 0.77, 95 % CI 0.56–1.04), and fibrosis (RR = 0.86, 95 % CI 0.72–1.03). Overall, the authors concluded that women taking tamoxifen, especially women younger than 50 years old, had reduced incidence of clinically detected benign breast disease and underwent fewer biopsies [53]. The current American Society of Clinical Oncology recommendation to discuss chemoprevention with women at increased 5-year risk for beast cancer supports consistent use of benign breast biopsy morphology to classify risk [54].

Benign breast disease is a common entity that places women at an elevated risk for breast cancer as evaluated and proven by the many studies from multiple countries included in this meta-analysis. Investigation of management strategies to determine which patients could potentially benefit from closer adherence to existing screening recommendations, from additional screening modalities, or from chemoprevention is needed.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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## References

1. Silvera S, Rohan T (2008) Benign proliferative epithelial disorders of the breast: a review of the epidemiologic evidence. Breast Cancer Res Treat 110:397–409
2. Wellings SR, Jensen HM, Marcum RG (1975) An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. J Natl Cancer Inst 55:231–273
3. Lee S, Mohsin SK, Mao S, Hilsenbeck SG, Medina D, Allred DC (2006) Hormones, receptors, and growth in hyperplastic enlarged lobular units: early potential precursors of breast cancer. Breast Cancer Res 8:R6
4. Berryhill GE, Gloviczki JM, Trott JF, Aimo L, Kraft J, Cardiff RD, Paul CT, Petrie WK, Lock AL, Hovey RC (2012) Diet-induced metabolic change induces estrogen-independent allometric mammary growth. Proc Natl Acad Sci USA 109:16294–16299
5. Su X, Tamimi RM, Collins LC, Baer HJ, Cho E, Sampson L, Willett WC, Schnitt SJ, Connolly JL, Rosner BA, Colditz GA (2010) Intake of fiber and nuts during adolescence and incidence of proliferative benign breast disease. Cancer Causes Control 21:1033–1046
6. Berkey CS, Willett WC, Frazier AL, Rosner B, Tamimi RM, Colditz GA (2011) Prospective study of growth and development in older girls and risk of benign breast disease in young women. Cancer 117:1612–1620
7. Berkey CS, Willett WC, Frazier AL, Rosner B, Tamimi RM, Rockett HR, Colditz GA (2010) Prospective study of adolescent alcohol consumption and risk of benign breast disease in young women. Pediatrics 125:e1081–e1087
8. Jung MM, Colditz GA, Collins LC, Schnitt SJ, Connolly JL, Tamimi RM (2011) Lifetime physical activity and the incidence of proliferative benign breast disease. Cancer Causes Control 22:1297–1305
9. Liu Y, Tamimi RM, Berkey CS, Willett WC, Collins LC, Schnitt SJ, Connolly JL, Colditz GA (2012) Intakes of alcohol and folate during adolescence and risk of proliferative benign breast disease. Pediatrics 129:e1192–e1198
10. Liu Y, Colditz GA, Rosner B, Berkey CS, Collins LC, Schnitt SJ, Connolly JL, Chen WY, Willett WC, Tamimi RM (2013) Alcohol intake between menarche and first pregnancy: a prospective study of breast cancer risk. J Natl Cancer Inst 105:1571–1578
11. Friedenreich C, Bryant H, Alexander F, Hugh J, Danyluk J, Page D (2000) Risk factors for benign proliferative breast disease. Int J Epidemiol 29:637–644
12. Elmore JG, Gigerenzer G (2005) Benign breast disease—the risks of communicating risk. N Engl J Med 353:297–299
13. Krieger N, Hiatt RA (1992) 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 135:619–631
14. Colditz GA, Rosner B (2000) Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the nurses' health study. Am J Epidemiol 152:950–964
15. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ (2007) Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia. Cancer 109:180–187
16. Page DL, Dupont WD, Rogers LW, Rados MS (1985) Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer 55:2698–2708
17. Dupont WD, Page DL (1987) Breast cancer risk associated with proliferative disease, age at first birth, and a family history of breast cancer. Am J Epidemiol 125:769–779
18. Carter CL, Corle DK, Micozzi MS, Schatzkin A, Taylor PR (1988) A prospective study of the development of breast cancer in 16,692 women with benign breast disease. Am J Epidemiol 128:467–477

19. Jensen RA, Page DL, Dupont WD, Rogers LW (1989) Invasive breast cancer risk in women with sclerosing adenosis. Cancer 64:1977–1983
20. Ashbeck EL, Rosenberg RD, Stauber PM, Key CR (2007) Benign breast biopsy diagnosis and subsequent risk of breast cancer. Cancer Epidemiol Biomark Prev 16:467–472
21. Bodian CA, Perzin KH, Lattes R, Hoffmann P, Abernathy TG (1993) Prognostic significance of benign proliferative breast disease. Cancer 71:3896–3907
22. Boulos FI, Dupont WD, Simpson JF, Schuyler PA, Sanders ME, Freudenthal ME, Page DL (2008) Histologic associations and long-term cancer risk in columnar cell lesions of the breast. Cancer 113:2415–2421
23. Dorjgochoo T, Deming S, Gao Y-T, Lu W, Zheng Y, Ruan Z, Zheng W, Shu X (2008) History of benign breast disease and risk of breast cancer among women in china: a case–control study. Cancer Causes Control 19:819–828
24. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD Jr, Rados MS, Schuyler PA (1994) Long-term risk of breast cancer in women with fibroadenoma. N Engl J Med 331:10–15
25. Dupont WD, Parl FF, Hartmann WH, Brinton LA, Winfield AC, Worrell JA, Schuyler PA, Plummer WD (1993) Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer 71:1258–1265
26. Goldacre MJ, Abisgold JD, Yeates DG, Vessey MP (2010) Benign breast disease and subsequent breast cancer: English record linkage studies. J Public Health (Oxf) 32:565–571
27. 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 (2005) Benign breast disease and the risk of breast cancer. N Engl J Med 353:229–237
28. Helmrich SP, Shapiro S, Rosenberg L, Kaufman DW, Slone D, Bain C, Miettinen OS, Stolley PD, Rosenshein NB, Knapp RC, Leavitt T, Schottenfeld D, Engle RL, Levy M (1983) Risk factors for breast cancer. Am J Epidemiol 117:35–45
29. Hill DA, Preston-Martin S, Ross RK, Bernstein L (2002) Medical radiation, family history of cancer, and benign breast disease in relation to breast cancer risk in young women, USA. Cancer Causes Control 13:711–718
30. Hutchinson WB, Thomas DB, Hamlin WB, Roth GJ, Peterson AV, Williams B (1980) Risk of breast cancer in women with benign breast disease. J Natl Cancer Inst 65:13–20
31. Kabat GC, Jones JG, Olson N, Negassa A, Duggan C, Ginsberg M, Kandel RA, Glass AG, Rohan TE (2010) A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer. Cancer Causes Control 21:821–828
32. Levi F, Randimbison L, Te VC, La Vecchia C (1994) Incidence of breast cancer in women with fibroadenoma. Int J Cancer 57:681–683
33. Lewis JT, Hartmann LC, Vierkant RA, Maloney SD, Shane Pankratz V, Allers TM, Frost MH, Visscher DW (2006) An analysis of breast cancer risk in women with single, multiple, and atypical papilloma. Am J Surg Pathol 30:665–672
34. McDivitt RW, Stevensm JA, Lee NC, Wingo PA, Rubin GL, Gersell D (1992) Histologic types of benign breast disease and the risk for breast cancer. Cancer 69:1408–1414
35. Minami Y, Ohuchi N, Taeda Y, Takano A, Fukao A, Satomi S, Hisamichi S (1999) Risk of breast cancer in Japanese women with benign breast disease. Jpn J Cancer Res 90:600–606
36. Nomura Y, Tashiro H, Katsuda Y (1993) Benign breast disease as a breast cancer risk in Japanese women. Jpn J Cancer Res 84:938–944
37. Page DL, Schuyler PA, Dupont WD, Jensen RA, Plummer WD Jr, Simpson JF (2003) Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: a retrospective cohort study. Lancet 361:125–129
38. Palli D, Turco MRD, Simoncini R, Bianchi S (1991) Benign breast disease and breast cancer: a case-control study in a cohort in Italy. Int J Cancer 47:703–706
39. Sakr R, Rouzier R, Salem C, Antoine M, Chopier J, Darai E, Uzan S (2008) Risk of breast cancer associated with papilloma. Eur J Surg Oncol 34:1304–1308
40. Shaaban AM, Sloane JP, West CR, Moore FR, Jarvis C, Williams EMI, Foster CS (2002) Histopathologic types of benign breast lesions and the risk of breast cancer: case-control study. Am J Surg Pathol 26:421–430
41. Wang J, Costantino JP, Tan-Chiu E, Wickerham DL, Paik S, Wolmark N (2004) Lower-category benign breast disease and the risk of invasive breast cancer. J Natl Cancer Inst 96:616–620
42. Worsham MJ, Raju U, Lu M, Kapke A, Botttrell A, Cheng J, Shah V, Savera A, Wolman SR (2009) Risk factors for breast cancer from benign breast disease in a diverse population. Breast Cancer Res Treat 118:1–7
43. Worsham MJ, Raju U, Lu M, Kapke A, Cheng J, Wolman SR (2007) Multiplicity of benign breast lesions is a risk factor for progression to breast cancer. Clin Cancer Res 13:5474–5479
44. Wrensch MR, Petrakis NL, Miike R, King EB, Chew K, Neuhaus J, Lee MM, Rhys M (2001) Breast cancer risk in women with abnormal cytology in nipple aspirates of breast fluid. J Natl Cancer Inst 93:1791–1798
45. Laird NM, Mosteller F (1990) Some statistical methods for combining experimental results. Int J Technol Assess Health Care 6:5–30
46. Begg C, Berlin J (1988) Publication bias: a problem in interpreting medical data. J R Stat Soc A 151:419–463
47. McLaren BK, Schuyler PA, Sanders ME, Jensen RA, Simpson JF, Dupont WD, Page DL (2006) Excellent survival, cancer type, and Nottingham grade after atypical lobular hyperplasia on initial breast biopsy. Cancer 107:1227–1233
48. Ghys R (1986) Natural history of benign and malignant breast tumors seen in a screening center. 15-year retrospective study. Cancer 57:1618–1626
49. Pankratz VS, Hartmann LC, Degnim AC, Vierkant RA, Ghosh K, Vachon CM, Frost MH, Maloney SD, Reynolds C, Boughey JC (2008) Assessment of the accuracy of the gail model in women with atypical hyperplasia. J Clin Oncol 26:5374–5379
50. Tamimi RM, Rosner B, Colditz GA (2010) Evaluation of a breast cancer risk prediction model expanded to include category of prior benign breast disease lesion. Cancer 116:4944–4953
51. Khan SA, Rogers MAM, Khurana KK, Meguid MM, Numann PJ (1998) Estrogen receptor expression in benign breast epithelium and breast cancer risk. J Natl Cancer Inst 90:37–42
52. Schnitt SJ (2001) Benign breast disease and breast cancer risk: potential role for antiestrogens. Clin Cancer Res 7:4419s–4422s discussion 4411s–4412s
53. Tan-Chiu E, Wang J, Costantino JP, Paik S, Butch C, Wickerham DL, Fisher B, Wolmark N (2003) Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. J Natl Cancer Inst 95:302–307
54. Visvanathan K, Hurley P, Bantug E, Brown P, Col NF, Cuzick J, Davidson NE, Decensi A, Fabian C, Ford L, Garber J, Katapodi M, Kramer B, Morrow M, Parker B, Runowicz C, Vogel VG 3rd, Wade JL, Lippman SM (2013) Use of pharmacologic interventions for breast cancer risk reduction: American society of clinical oncology clinical practice guideline. J Clin Oncol 31:2942–2962