Lower-Category Benign Breast Disease and the Risk of Invasive Breast Cancer

Jiping Wang, Joseph P. Costantino, Elizabeth Tan-Chiu, D. Lawrence Wickerham, Soonmyung Paik, Norman Wolmark

Background: **The risk of invasive breast cancer associated with benign breast disease (BBD) other than atypical hyperplasia and *in situ* breast cancer, especially with nonproliferative diagnosis, has not been explored extensively. This report evaluates the risk of breast cancer associated with this lower-category BBD (LC-BBD). Methods: 11 307 women without prior history of atypical hyperplasia or *in situ* breast cancer at randomization (1992–1997) were identified from the cohort of the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention Trial. Pathologic findings from breast biopsy reports through August 2002 were reviewed, and Cox proportional hazards models were used to determine the relative risks (RRs) of breast cancer with 95% confidence intervals (CIs). The relative risks of breast cancer for LC-BBD were adjusted for treatment and for breast cancer risk as determined by the modified Gail model. *Results:* Of the 11 307 women, 1376 had LC-BBD, of whom 47 developed breast cancer, and of the 9931 women without LC-BBD, 291 developed breast cancer. The RR of breast cancer for women with LC-BBD relative to women without LC-BBD was 1.60 (95% CI = 1.17 to 2.19). Among women 50 years of age and older, the RR of breast cancer for those with LC-BBD was 1.95 (95% CI = 1.29 to 2.93). After adjustment for treatment and breast cancer risk, the RR of breast cancer for women with LC-BBD was 1.41 (95% CI = 1.03 to 1.94). *Conclusions:* Women with LC-BBD had a statistically significant increased risk of breast cancer. The elevation of breast cancer risk was especially evident in women 50 years of age and older. Furthermore, this risk was independent of that associated with key epidemiologic breast cancer risk factors. [J Natl Cancer Inst 2004;96:616–20]**

The term benign breast disease (BBD) is used to describe a composite of several clinical diagnoses noted at breast biopsy. In 1985, the Cancer Committee of the College of American Pathologists reached a consensus on the type of pathologic findings included in BBD and on the grouping of the pathologic diagnoses into categories relative to the degree of invasive breast cancer risk likely to be associated with each category *(1).* In 1998, Fitzgibbons et al. *(2)* reported an updated version of the consensus definitions. The categories of risk and the pathologic diagnoses included in each category as most recently defined are presented in Table 1.

Several authors have studied the risk of breast cancer associated with BBD. The largest body of information relating BBD to breast cancer has come from data collected as part of the follow-up of women participating in cohort studies *(3,4).* Dupont and Page *(3)* reported the relative risk (RR) of breast cancer in women with proliferative breast diseases in a retrospective cohort study. Carter et al. *(4)* also reported the RR for breast cancer in women diagnosed with BBD in the Breast Cancer Detection and Demonstration Project. Findings regarding BBD are also available from another large study, the Nurses Health Study. Using a nested case–control methodology, London et al. *(5)* reported estimates of RR for subsets of BBD from this population. Several other groups have studied BBD in smaller populations *(6–12).*

In their assessment of the association between BBD and breast cancer, some authors have recognized the potential for confounding in the estimates of breast cancer risk and have adjusted for or stratified some of the key epidemiologic factors known to be associated with breast cancer risk. However, none of these authors has fully explored the independence of BBD in breast cancer risk from the known breast cancer risk factors by including adjustment for the full complement of breast cancer risk factors used in the Gail model *(13)* (such as age at menarche, number of first-degree relatives diagnosed with breast cancer, age at menopause, age at first live birth, and number of previous breast biopsies). Adjustment for all key risk factors is critical for determining the independent nature of BBD as a predictor of breast cancer and for estimating the magnitude of risk associated with specific pathologic diagnoses of BBD. This type of adjustment is particularly important for assessing the independent nature of the risk associated with the pathologic diagnoses of BBD that are included in the College of American Pathologists' BBD categories 1 and 2 (Table 1), for which the available RR estimates are lower than for those in categories 3 and 4 (e.g., atypical hyperplasia and *in situ* disease).

In general, the emphasis of breast cancer risk determination associated with BBD has been on disease associated with the upper categories of BBD (i.e., categories 3 and 4). The focus of this report is both to quantify the risk of breast cancer associated with the pathologic types of BBD in the two lower categories—to which we refer as lower-category benign breast disease (LC-BBD)—and to determine whether LC-BBD is an independent predictor of breast cancer after adjustment for the full set of key epidemiologic factors known to be associated with breast cancer risk. We used data from the Breast Cancer Prevention

Affiliations of authors: Biostatistical Center, National Surgical Breast and Bowel Project and Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA (JW, JPC); Cancer Research Network, Plantation, FL (ETC); Operations Office, National Surgical Breast and Bowel Project and Department of Surgical Oncology Allegheny General Hospital, Pittsburgh, PA (DLW, NW); Division of Pathology, National Surgical Breast and Bowel Project and Department of Pathology, Allegheny General Hospital (SP).

Correspondence to: Jiping Wang, MD, PhD, Biostatistical Center, National Surgical Breast and Bowel Project, University of Pittsburgh, 201 N. Craig St., Ste. 350, Pittsburgh, PA 15213 (e-mail: wang@nsabp.pitt.edu).

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Table 1. Categories of the College of American Pathologist classification of benign breast disease *(2)*

Pathologic category	Level of increased risk for invasive breast cancer	Pathological types included in the category
1	No increase	Adenosis (other than sclerosing adenosis) Ductal ectasia Fibroadenoma without complex features Fibrosis Mastitis Mild hyperplasia without atypia Ordinary cysts (gross or microscopic) Simple apocrine metaplasia (no associated hyperplasia or adenosis) Squamous metaplasia
2	Slightly increased	Fibroadenoma with complex features Moderate or florid hyperplasia without atypia Sclerosing adenosis, Solitary papilloma without coexistent atypical hyperplasia
3	Moderately increased	Atypical ductal hyperplasia Atypical lobular hyperplasia
4	Markedly increased	Ductal carcinoma *in situ* Lobular carcinoma *in situ*

Trial (BCPT), Protocol P-1, of the National Surgical Adjuvant Breast and Bowel Project. This trial, in which women at increased risk of breast cancer were randomly assigned to 5 years of either tamoxifen or placebo, represents one of the largest studies in recent history in which healthy women at high risk for breast cancer have been prospectively followed and the diagnosis of all breast biopsies has been systematically reported *(14)*. Information from this study provides a prospectively collected source of data to evaluate the relationship between LC-BBD and breast cancer, while adjusting for the full compliment of key breast cancer risk factors by using the composite breast cancer risk estimates obtained for each participant from the modified Gail model *(13)*.

Subjects and Methods

The details of the study design of the BCPT have been described previously *(14)*. The protocol was approved by the institutional review board of the University of Pittsburgh, and written informed consent was obtained from each participant. Women were eligible for participation in the BCPT if they were 60 years of age or older, if they were between the ages of 35 and 59 years and had a 5-year predicted risk for breast cancer of at least 1.66%, or if they had a history of lobular carcinoma *in situ*. Of the 13 388 women randomly assigned in the BCPT between April 1992 and March 1998, 11 307 women were identified who did not have a prior history of atypical hyperplasia or *in situ* breast cancer at the time of randomization. As part of the follow-up in the BCPT, these women received semiannual physical breast examinations and annual bilateral mammograms. The BCPT protocol required the reporting of all findings regarding these procedures and also the submission of copies of all mammography and pathology reports to document the findings. The pathologic findings from the reports of breast biopsies were prospectively reviewed by the NSABP medical research staff, and findings regarding the type of benign breast disease and invasive breast cancer were coded as part of the NSABP database for the BCPT. The pathology reports for case patients with hyperplasia without atypia and reporting fibroadenoma were not always sufficiently detailed for us to determine whether the degree of hyperplasia was mild or moderate or to determine the presence or absence of complex features with fibroadenoma; that is, it is difficult to differentiate category 1 from category 2 on the basis of pathology reports. Hence, this report focuses on assessing the association between breast cancer and LC-BBD, including cyst; adenosis; duct ectasia; fibrosis; metaplasia; fibroadenoma; mild, moderate, or florid hyperplasia without atypia; and papilloma.

An initial analysis was performed based on a set of data that was limited to the information obtained while the participants were under blinded follow-up; that is, before the announcement of findings from the trial (through March 1998). The results of this initial analysis provided no evidence of an interaction between treatment and LC-BBD in terms of LC-BBD as a marker for breast cancer. Thus, to increase the number of LC-BBD and breast cancer events for study and to improve the statistical power of the assessment, a subsequent analysis was undertaken based on all follow-up data from the BCPT received and processed by August 31, 2002. The findings presented in this report are based on the analysis of the extended follow-up data for which the mean follow-up time is 79 months.

Statistical Analysis

The primary method of analysis was Cox proportional hazard modeling of time to diagnosis of breast cancer. In this modeling, the first diagnosis of LC-BBD was incorporated as a time-dependent covariate. Women who developed atypical hyperplasia or noninvasive breast cancer were censored at the time of these events. The relative risk of breast cancer and the 95% confidence interval (CI) for the relative risk were derived from the parameter estimates of the Cox modeling. To determine whether LC-BBD is an independent marker of breast cancer, multivariable Cox modeling was performed including treatment and level of breast cancer risk as additional covariates. The proportional hazards assumption for treatment and level of breast cancer risk was verified by using Grambsch and Therneau's method *(15)*. Adjustment for level of breast cancer risk was achieved by including each woman's 5-year risk score as determined from the modified Gail model *(13)*. The use of this score provided a parsimonious means to adjust for seven breast cancer risk factors (age, race, age at menarche, age at first live birth, family history of breast cancer, number of breast biopsies, and history of atypical hyperplasia) as one parameter in the modeling. For women who did not undergo a biopsy, the 5-year risk score that was incorporated in the modeling was that determined at randomization into the BCPT. For those who experienced a biopsy, the 5-year risk score used in the modeling was that determined at the time of the first diagnosis of LC-BBD. Average annual rates of breast cancer diagnosis were calculated by dividing the number of observed events by the number of observed event-specific person-years of follow-up. The person-years at risk for the determination of the breast cancer diagnosis rate in women with LC-BBD were calculated from time of first confirmed LC-BBD biopsy to time of developing breast cancer or to time of last follow-up. The person-years at risk for the determination of the breast cancer diagnosis rate for those without LC-BBD were calculated as the sum of the time from

Table 2. Annual rate of invasive breast cancer among women in the Breast Cancer Prevention Trial by age group and diagnosis of lower-category benign breast disease (LC-BBD)

Age	LC-BBD	No. of women	No. of events*	Rate per 1000 women	Relative risk† (95% CI)
≤49	Yes	686	20	5.99	1.26 (0.78 to 2.05)
	No	3519	107	4.62	
≥50	Yes	690	27	8.46	1.95 (1.29 to 2.93)
	No	6412	184	4.28	
Total	Yes	1376	47	7.20	1.60 (1.17 to 2.19)
	No	9931	291	4.40	

*Event is defined as diagnosis of invasive breast cancer.
†Relative risks are estimated from Cox model and are relative to women without BBD. CI = confidence interval.

randomization to the time of developing breast cancer or to the time of last follow-up (for women who never developed LC-BBD) and time from randomization to time of first confirmed LC-BBD biopsy (for women who did develop LC-BBD).

Results

Of the 11 307 women included in this analysis, 1376 women were diagnosed with LC-BBD during the course of follow-up, of whom 47 were subsequently diagnosed with breast cancer (Table 2). Overall, the average annual diagnosis rate of breast cancer for women with LC-BBD was 7.20 per 1000. Among the 9931 women who were not diagnosed with LC-BBD, 291 developed breast cancer, for an average annual rate of 4.40 per 1000. When comparing the rates of breast cancer among those with LC-BBD with the rates of those without disease, the relative risk of breast cancer for women with a prior diagnosis of LC-BBD was statistically significantly elevated, at 1.60 (95% CI = 1.17 to 2.19).

When considering age at the initiation of follow-up, the relative risk of breast cancer for LC-BBD was elevated for all ages combined. However, the increase was statistically significant only among women 50 years of age and older. In this age group, annual rates of breast cancer for women with and without LC-BBD were 8.46 per 1000 and 4.28 per 1000, respectively (RR = 1.95, 95% CI = 1.29 to 2.93). Among those patients under 50 years of age, the annual rates of breast cancer for women with and without disease were 5.99 per 1000 and 4.62 per 1000, respectively (RR = 1.26, 95% CI = 0.78 to 2.05).

As would be expected, women in the tamoxifen group had a lower risk of breast cancer than did those in the placebo group. This difference was evident even when the women were stratified by LC-BBD status (Table 3). A statistically significant effect of LC-BBD was evident within each treatment group, and the magnitude of effect within each treatment group was similar. Among the placebo group, annual rates of breast cancer were 8.04 per 1000 for women with LC-BBD and 5.43 per 1000 among those without LC-BBD. Among the tamoxifen group, annual rates of breast cancer were 6.30 per 1000 and 3.52 per 1000 for women with and without LC-BBD, respectively. The relative risk of breast cancer for women with LC-BBD was 1.46 (95% CI = 0.97 to 2.21) in the placebo group and 1.69 (95% CI = 1.05 to 2.73) in the tamoxifen group.

After adjustment for treatment and breast cancer risk factors, LC-BBD was a statistically significant independent marker for the prediction of breast cancer (Table 4). The point estimates for the relative risk of breast cancer associated with LC-BBD (model 1) changed only slightly when adjusting for treatment alone or when adjusting for treatment and breast cancer risk factors. With adjustment for treatment (model 2), the relative risk was 1.55 (95% CI = 1.14 to 2.12). With adjustment for both treatment and breast cancer risk factors (model 3), the relative risk was 1.41 (95% CI = 1.03 to 1.94).

The distribution of LC-BBD by the specific type of pathologic finding is presented in Table 5. The diagnosis of cysts without mention of any other pathological finding was the most frequent diagnosis, occurring among 674 (49.0%) of those who had a BBD diagnosis. A diagnosis of multiple concurrent pathological types of disease was the next most frequent finding, occurring among 523 women (38.0%). Of the women with multiple concurrent diagnoses, 256 had two concurrent forms of LC-BBD reported, 139 had three concurrent forms reported, 71 had four forms reported, and 57 had five or more forms reported. Because the number of breast cancer events was very small for all specific single types of LC-BBD except cysts, cysts were the only pathologic type for which rate determination and Cox modeling was performed (Table 6). The average annual rate of breast cancer among those diagnosed with cysts was 8.07 per 1000. The magnitude of breast cancer risk associated with a diagnosis of cyst was very similar to that found for all women with LC-BBD combined. For this pathologic finding, the crude

Table 3. Annual rate of invasive breast cancer among women in the Breast Cancer Prevention Trial by treatment group and diagnosis of lower-category benign breast disease (LC-BBD)

Treatment	LC-BBD	No. of women	No. of events*	Rate per 1000 women	Relative risk† (95% CI)
Placebo	Yes	775	27	8.04	1.46 (0.97 to 2.21)
	No	4871	165	5.43	
Tamoxifen	Yes	601	20	6.30	1.69 (1.05 to 2.73)
	No	5060	123	3.52	

*Event is defined as diagnosis of invasive breast cancer.
†Relative risks are estimated from Cox model and are relative to women without BBD. CI = confidence interval.

Table 4. Results of multivariable Cox modeling to predict the risk of invasive breast cancer among women in the Breast Cancer Prevention Trial incorporating the diagnosis of lower category benign breast disease (LC-BBD)

	Model 1*		Model 2*		Model 3*	
Covariates	RR†	95% CI	RR†	95% CI	RR†	95% CI
LC-BBD	1.60	(1.17 to 2.19)	1.55	(1.14 to 2.12)	1.41	(1.03 to 1.94)
Treatment‡§			0.63	(0.50 to 0.79)	0.63	(0.50 to 0.79)
Breast cancer risk§					1.12	(1.06 to 1.19)

*Model 1 includes only LC-BBD. Model 2 includes LC-BBD and treatment. Model 3 includes LC-BBD, treatment, and breast cancer risk.

†RR = relative risk, CI = confidence interval. The reference category was women without BBD.

‡Point estimates for the relative risk of breast cancer associated with treatment and breast cancer risk independent of LC-BBD are shown.

§Five-year risk determined from the Gail model *(13)* incorporating age, race, age at first live birth, age at menarche, number of first-degree relatives with a history of breast cancer and number of breast biopsies.

relative risk was 1.79 (95% CI=1.20 to 2.68) and the adjusted relative risk was 1.60 (95% CI=1.07 to 2.40).

Discussion

When exploring the association between BBD and breast cancer, the focus has most often been on atypical hyperplasia and *in situ* breast cancer *(6–12)*. Women with a diagnosis of either of these two forms of BBD are generally recognized as being at an elevated risk for the development of breast cancer. Although nonproliferative lesions account for 70% of breast biopsies performed *(5)*, the association between breast cancer and LC-BBD has not been explored to the same degree as that between atypical hyperplasia and *in situ* disease. As a result, the potential increased breast cancer risk associated with LC-BBD is not always appreciated. The data from Bodian et al. *(6)*, Carter et al. *(4)*, and London et al. *(5)* indicate that women with LC-BBD do have an increased risk of breast cancer. However, the study by Bodian et al. *(6)* did not consider the influence of confounding that could be associated with any of the known key epidemiological breast cancer risk factors. The assessment by Carter et al. *(4)* included stratification for family history but not for any other key risk factors. When comparing those patients with and those without a history of proliferative breast disease, London et al. *(5)* provided the most comprehensive form of adjustment reported to date. They found that an increased risk of breast cancer persists among women who have experienced proliferative disease even after adjustment for family history, menopause status, age at menarche, age at first birth, and parity.

Table 5. Frequency of invasive breast cancer among women in the Breast Cancer Prevention Trial by types of lower-category benign breast disease (LC-BBD)

Type of LC-BBD	No. of women with diagnosis	No. of invasive breast cancer cases
Adenosis	12	0
Cyst	674	26
Ductal ectasia	5	0
Fibroadenoma	50	2
Fibrosis	61	1
Hyperplasia without atypia	27	3
Metaplasia	24	0
More than one type	523	15
Two concurrent types	256	10
Three concurrent types	139	2
Four concurrent types	71	2
Five or more concurrent types	57	1
Total	1376	47

The results from our study are consistent with those of Carter, Bodian, and London and indicate that women with LC-BBD do have a statistically significant increased risk of breast cancer. Furthermore, our findings confirm those of London et al. *(5)* and indicate that the risk of breast cancer associated with LC-BBD is independent of that associated with the key epidemiologic breast cancer risk factors. After adjustment for treatment and breast cancer risk, women in our study who had a diagnosis of LC-BBD had a risk of breast cancer that was 41% higher than that of women who did not experience breast disease.

Our data also indicate that women diagnosed with a mammary cyst have an increased breast cancer risk. An elevated risk of breast cancer associated with a diagnosis of a cyst has been indicated by studies of case series *(16–18)*. However, these studies used rates from the general population for comparison and did not consider the confounding effect of epidemiologic factors affecting breast cancer risk. Our data, which are adjusted for confounding factors, indicate that a diagnosis of a cyst is an independent risk factor associated with breast cancer and that the risk of breast cancer in patients with cysts is about 60% higher than the risk in those who have no form of breast disease. This finding indicates that women with LC-BBD, particularly those with cysts, should be considered at increased risk for the development of breast cancer and should be followed accordingly.

Only a moderate number of breast cancer cases were diagnosed among women who developed LC-BBD during the course of follow-up in the BCPT. Additional studies on larger datasets that include the ascertainment of complete breast cancer risk factor profiles are needed to further quantify the magnitude of independent breast cancer risk associated with LC-BBD. Additional studies are also needed to separately quantify the level of breast cancer risk associated with each of the LC-BBD pathologic types. Although we had originally hoped to develop separate estimates for several other pathologic types, because the number of breast cancer events was too small for the other LC-BBD categories, we were able only to determine estimates of breast cancer risk for cysts. In addition, it was not always possible for us to determine whether the degree of hyperplasia was mild or moderate or to make a determination regarding the presence or absence of complex features with fibroadenoma (fibroadenomas with or without cysts greater than 3.0 mm, sclerosing adenosis, calcifications, or papillary apocrine changes) *(2)*. These are limitations inherent in using data reported from multiple community pathologists without having biopsy material for central review. An additional limitation of

Table 6. Annual rate of invasive breast cancer among women in the Breast Cancer Prevention Trial among those diagnosed with cysts and other types of lower-category benign breast disease (LC-BBD)

Type of LC-BBD	No. of women	No. of events	Rate per 1000 women	Relative risk* (95% CI)	Adjusted relative risk (95% CI)†
Cysts	674	26	8.07	1.79 (1.20 to 2.68)	1.60 (1.07 to 2.40)
Other LC-BBD‡	702	21	6.35	1.42 (0.91 to 2.21)	1.24 (0.79 to 1.95)

*The reference category is women without BBD.

†Adjusted for treatment and five-year risk determined from the Gail model incorporating age, race, age at first live birth, age at menarche, number of first-degree relatives with a history of breast cancer and number of breast biopsies.

‡Other LC-BBD includes adenosis, ductal ectasia, fibroadenoma, fibrosis, hyperplasia without atypia, metaplasia and papilloma.

using this type of data is that not all pathologists use standardized criteria for reviewing biopsies. However, estimating breast cancer risk on the basis of the diagnoses of community pathologists provides risk values that relate directly to the actual pathologic diagnoses that are used as the basis for decision-making in clinical practice for women at high risk of breast cancer.

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Notes

Dr. Wickerham is a member of the Speaker's Bureau for Astra Zeneca.

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