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History of benign breast disease and risk of breast cancer among women in China: a case control study

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Abstract

Background: Data from the Shanghai Breast Cancer Study were analyzed to evaluate the relationship between benign breast disease (BBD) and breast cancer among Chinese women with a self-report of physician-diagnosed BBD.

Methods: Study participants consisted of 3,452 breast cancer cases and 3,474 population controls recruited by the Shanghai Breast Cancer Study. In-person interviews were conducted to collect information on demographics and suspected risk factors for breast cancer, including a detailed history of BBD. Unconditional logistic regression was used to derive adjusted odds ratios (OR_{adj}) and 95% confidence intervals (CI) for the association between self-reported BBD and breast cancer.

Results: Women with breast cancer were significantly more likely to have a self-reported history of BBD including lobular proliferation (OR_{adj}=1.6; 95% CI 1.4-1.8), fibroadenoma (OR_{adj}=1.9; 95% CI 1.5-2.3), and other BBD (OR_{adj}=1.6; 95% CI 1.3-2.1). Breast cancer risk was lower for surgically treated fibroadenoma as compared to non-surgically treated and higher for other BBDs that were surgically treated versus non-surgically treated.

Conclusions: Our results suggest that personal history of BBD is associated with an increased risk of future breast cancer among women in China. Surgical intervention for fibroadenoma may reduce the risk.

Keywords

benign breast diseases; breast cancer; risk factor; case control-study; women; China

Background

Worldwide, breast cancer is the most common form of cancer and is a leading cause of cancer deaths among women. The highest breast cancer rates can be found in North America and Northern Europe, while intermediate levels are reported in Western Europe, Oceania, Scandinavia, and Israel (1,2). The regions with the lowest rates are Eastern Europe, South America, and Asia. However, from the 1970s to the 1990s, breast cancer incidence had risen

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Competing interest

The authors declare that they have no competing interests.

30-40% in most countries, including China, where the rate has risen particularly among women aged 50 or older (3).

Benign breast disease (BBD) is very common among women of reproductive age (4,5). BBD is a well known risk factor for breast cancer, although the magnitude of the association varies by lesion type (6-8). BBD represents a composite of clinical and histopathological diagnoses of breast tissue lesions including developmental abnormalities, inflammatory lesions, epithelial and stromal proliferations, and neoplasms. Based on these types of pathologic diagnoses for BBD, the Cancer Committee of the College of American Pathologists recommended 4 risk categories of BBD in 1985, Appendix I (9,10). The association of the high risk categories (3 and 4) of BBD (eg, atypical hyperplasia and carcinoma in situ) with invasive breast cancer risk is well established (8,11,12). However, the ANDI (Aberrations of Normal Development and Involution) classification of BBD and recent studies have suggested that the risk of breast cancer may also be associated with the two lower risk categories (1 and 2) of BBD that include fibroadenoma, cysts, mastitis, fibrosis, adenosis and hyperplasia without atypia (10,13,14). However, there is no unequivocal classification for all BBD that is commonly accepted by clinicians, pathologists and epidemiologists, since the mechanisms behind the development of benign breast lesions are unclear (5,15-17).

Given that there is a paucity of information regarding the association between lower categories of BBD and breast cancer risk, we investigated the relationship between a self-report of physician-diagnosed BBD and breast cancer risk using data from the Shanghai Breast Cancer Study, a large population-based case-control study conducted in an area where there are no nationally-recognized screening guidelines or services for breast cancer.

Methods

The Shanghai Breast Cancer Study (SBCS) is a two-phase, population-based, case-control study of incident breast cancer conducted in Shanghai, China from August 1996 to March 1998 (Phase I) and from April 2002 to February 2005 (Phase II). Details of the SBCS have been described previously (3). Briefly, cases were identified through a rapid case-ascertainment system supplemented by the population-based Shanghai Cancer Registry. Diagnoses of cancer were confirmed through review of pathological slides and medical charts. Cases were ineligible for the study if they were not permanent residents of urban Shanghai or if they had a prior history of cancer. Controls were randomly selected from permanent female residents of the study area and frequency-matched to cases on age. A total of 3,452 cases and 3,474 controls were recruited in Phases I and II of the study. In Phase I, 1,455 (response rate: 91.1%) and 1,556 (90.3%) controls were recruited, while in Phase II 1,997 (83.7%) cases and 1,918 (70.4%) controls were recruited. The difference in response rates between the Phase I and Phase II studies was primarily due to the difference in age eligibility. The range of age eligibility for Phase I was 25 to 64 years, while for Phase II the range was 25 to 70 years. The median age for Phase I was 46 and for Phase II was 50. Older women were less likely to participate in the study because of the increased likelihood of co-morbidity. The lower rate of participation in Phase II may also be associated with the rapid socioeconomic development in China and emergence of door-to-door commercial marketing in China, which may have made women reluctant to respond to invitations to participate..

The study protocols were approved by the Institutional Review Boards of all institutes involved in the study, and written, informed consent was obtained from all participants. Information on demographic characteristics, menstrual and reproductive history, personal and family history of breast cancer, history of chronic diseases, various lifestyle and dietary habits was collected through in-person interviews. Detailed information was collected on BBD by asking: "Has your doctor ever told you that you had any of the following breast diseases, such as lobular

proliferation, fibroadenoma, cystic breast diseases and other?" (not including diagnoses made during the 12 months preceding the interview). Those who answered 'Yes' were considered subjects with 'any BBD' and were classified according to their types of BBD. The diagnostic term "lobular proliferation" is commonly used by physicians and pathologists in China and corresponds to the Western term "adenosis", which includes lobular (or blunt duct) adenosis, sclerosing adenosis, nodular adenosis, and microglandular adenosis (18,19). In the analyses, BBD were classified as follows: any BBD, lobular proliferation, fibroadenoma and cystic disease, and other BBD, which included all other types of BBD including both lower and higher risk categories of BBD (5,10,20). Women who reported multiple breast diseases were classified according to the disease that they were primarily treated for. Ideally, we would have confirmed participants' BBD diagnoses by pathology or medical chart review. However, most of the BBD cases were diagnosed 10 to 27 years prior to cancer diagnosis and the diagnoses were made by over 150 hospitals in Shanghai. Because the Chinese healthcare system is not organized around a primary care physician, validating the diagnosis of BBD would be extremely difficult logistically, as well as financially prohibitive. It is likely that women who had undergone surgery would be able to recall what type of disease they had better than those who did not receive surgery. We further analyzed BBD data by whether it was treated by surgery. Given the paucity of information on the risk of breast cancer associated with lower category BBD, we believe that self reports of BBD would provide valuable information that could serve as the foundation for additional research in this area. For each breast disease reported, participants were asked to report their age at first diagnosis and whether they had undergone prior breast surgical procedures (ever/never). We also investigated the association between length of time since the first diagnosis of BBD (less than median and equal or more than median years) and breast cancer risk.

Statistical tests were based on two-sided probability with a significant $\alpha < 0.05$. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) to measure the association between breast cancer risk and BBD. All OR estimates were adjusted for age (continuous), education, occupation and other risk factors previously identified in this population. These included age at menarche (continuous), age at first live birth (categorized), total breastfeeding duration (categorized in months: <1 , <12 , <24 and ≥ 24), body mass index (categorized), menopausal status (pre- and post-), exercise participation in the preceding 10 years (yes/no), first-degree family history of breast cancer (yes/no), oral contraceptive use (ever/never), and study phase (I and II). Age at BBD diagnosis and years since first diagnosis, the median age at first diagnosis, and median years since first diagnosis of BBD were categorized according to the distributions of controls.

Body mass index (BMI) and waist-to-hip ratio (WHR) were categorized by quartile distribution of the controls. We performed analyses stratified by menopausal status (pre- vs. postmenopausal), oral contraceptive use (yes/no), and BMI to see whether the association between BBD and breast cancer was modified by these factors. We used the global overweight and obesity cut-off points ($<25.0 \text{ kg/m}^2$ and $\geq 25.0 \text{ kg/m}^2$) recommended by the World Health Organization (WHO) (21) for the stratified analyses. We also used the BMI categories $<23.0 \text{ kg/m}^2$ and $\geq 23.0 \text{ kg/m}^2$ based on obesity classifications recommended by the WHO for Asians (21). Caloric intake, dietary intake (fruit, vegetables, meat), and abortion status were considered to be potential confounders, but were not included in the final models as they did not appreciably alter the odds ratios.

Women who reported never having a BBD were used as a reference group throughout. Tests for trend were performed by entering the categorical variables as continuous parameters in the model. Subjects with missing values accounted for less than 0.5% of the total and were excluded from all analyses. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Characteristics of cases and controls in the two study phases are presented in Table 1. The average age was 49.6 years for cases and 49.7 years for controls (n=6,926). Characteristics of the subjects in both phases were very similar overall, although participants in Phase II of the study were slightly older and more frequently postmenopausal. The latter difference can be attributed to the eligibility difference between the two phases of the study (25-64 years for Phase I and 25-70 years for Phase II). Compared to controls, cases were more likely to have higher educational or occupational attainments, earlier age at menarche, later age at menopause, be nulliparous, be of late age at first birth, be overweight or obese, have a family history of breast cancer among first-degree relatives, and have a personal history of BBD. Cases were also less likely to have breastfed or to have participated in sport activities. There was no difference in total energy or fruit and vegetable intake between cases and controls for both studies (data not presented).

Characteristics of participants with and without BBD were compared in the control population (Table 2). The prevalence of BBD in the control population was 26.3% (Phase I) and 33.4% (Phase II). Women with BBD were younger, had higher educational attainment, and were more likely to have a professional job than women without BBD. In both phases, those with BBD were also less likely to be postmenopausal or to be overweight or obese and were more likely to have had fewer children, to have had children at a later age, to have a short duration of breastfeeding, and to have had an abortion. In Phase II, compared to women without BBD, those with BBD were less likely to have used hormonal contraceptives, more likely to have a first-degree family history of breast cancer, and more likely to have engaged in exercise in the preceding 10 years. Energy intake, fruit and vegetable intake, and meat intake did not differ significantly between women with and without BBD in either study phase (data not shown).

The prevalence of BBD was 36.4% in this study population and was higher in Phase II (40.7%, 2002-2004) compared to Phase I (30.8%, 1996-1998). We found that lobular proliferation and fibroadenoma contributed most to this change in prevalence rates, particularly among breast cancer cases (data not shown in table). All subjects were classified by their benign breast conditions as follows: 2,057 (29.7%) lobular proliferation, 522 (7.5%) fibroadenoma, 38 (0.5%) cystic breast diseases, and 259 (3.7%) other (Table 3).

With the exception of cystic breast diseases, the prevalence of all types of BBD was more common among breast cancer cases than among controls. Among cases, prevalence rates were 34.8% for lobular proliferation, 9.7% for fibroadenoma, and 4.7% for other BBD, while the corresponding rates among controls were 24.6%, 5.4%, and 2.8%, respectively ($P<.0001$). The risk of developing breast cancer increased with number of types of BBD that a woman had with the adjusted odds ratios (OR_{adj}) being 2.6 (95% CI, 2.0-3.3) for having ≥ 2 types of BBD and 1.6 (95% CI, 1.4-1.7) for having only one type of BBD (Table 3). The OR_{adj} of developing breast cancer based on subtypes of BBD were: lobular proliferation: 1.6 (95% CI, 1.4-1.8), fibroadenoma: 1.9 (95% CI, 1.6-2.3), and other BBD: 1.6 (95% CI, 1.3-2.1). History of cystic breast disease was unrelated to breast cancer risk ($OR_{adj}=0.8$; 95% CI, 0.5-1.6).

The breast cancer risk associated with BBD varied little by age at first diagnosis of BBD or by years since first diagnosis of BBD (Table 3). Surgical treatment lowered the risk of breast cancer among women who had fibroadenoma, but had no effect on those with lobular proliferation or cystic breast disease. The increased risk associated with other BBD was mostly confined to those receiving surgical treatment ($OR_{adj}=1.2$; 95% CI, 0.8-1.9, without surgery and $OR_{adj}=1.9$; 95% CI, 1.4-2.7, with surgery).

To evaluate whether the effect of BBD on breast cancer risk differed among subgroups defined by indicators of estrogen exposure, we stratified the analysis by menopausal status, BMI, and

oral contraceptive use. The effects of BBD on breast cancer risk among subgroups defined by menopausal status are presented in Table 4. Both pre- and postmenopausal women with lobular proliferation, fibroadenoma and other BBD had an increased risk of breast cancer. The association was slightly stronger among premenopausal women, but tests for multiplicative interaction were only significant for other BBD. Benign breast diseases (except breast cysts) were associated with increased breast cancer risk across categories of BMI and tests for interaction were only significant for other BBD (data not shown). An inverse association was found between breast cancer risk and cystic breast disease among oral contraceptive users ($OR_{adj} = 0.2$, 95% CI 0.1-0.9; $P_{interaction} = 0.03$ among those with cystic breast disease, data not shown).

Discussion

To our knowledge, this is the first large population-based study investigating the association between self-reported, physician-diagnosed BBD and breast cancer risk among Chinese women, a population with a low incidence of breast cancer as compared to women in Western countries. In this group of women, lobular proliferation (29.7%) followed by fibroadenoma (7.5%) were the most frequently identified types of BBD. We found that participants with BBD shared similar demographic and breast cancer-related risk factors with breast cancer patients, including higher educational and occupational levels, early menarche, no or few live births, late menopause, short breastfeeding duration, high BMI, high proportion of family history of breast cancer among first degree of relatives (22-24), and low proportion of oral contraceptive use (10,25).

Consistent with previous cohort (6,22) and case-control studies in other populations (10,26), we found an increase in the risk of breast cancer among women reporting a history of BBD, especially women with fibroadenoma and lobular proliferation (10,26-30). Hormonal factors, particularly the relationship between hyperestrogenism and fibroadenoma, have been implicated in the development of BBD by previous studies (30-34). Thus, it is likely that fibroadenoma, which develops during the reproductive lifespan of women due to excess hormone exposure or other factors, is in the breast cancer development pathway. Consistent with other studies (28,30), we found that women with fibroadenoma who have undergone surgical treatment are two times less likely to develop breast cancer as compared to those who did not undergo surgery for the same disease. The increased risk of breast cancer among those surgically treated for 'other BBD' in this study may imply that women with higher risk categories of BBD are highly susceptible to breast cancer as has been reported previously (11,20,35). Future studies may need to address whether early detection and intervention for any type of BBD reduces the risk breast cancer and should be recommended.

Studies of the relationship between cysts and breast cancer have produced conflicting results. An adverse association between cystic breast disease and breast cancer has been previously reported (10,33,36). However, in the current study, we found an inverse association of cystic breast disease with breast cancer only among oral contraceptive users. It has been well documented that the incidence of BBD decreases with oral contraceptive use (10,25,33,37), although the mechanism by which oral contraceptives reduce risk is unknown (17,33,38). We speculate that oral contraceptives may suppress hyperestrogenism, which may be responsible for the development of breast cysts as noted in these previous reports (33,34,39).

Unlike the findings of Wang et al and other studies (6,10,11,35), we found that menopausal status did not modify the association of breast cancer risk with BBD. However, these previous studies focused mainly on atypical hyperplasia or other high-risk category BBD. In several studies, the risk of breast cancer was higher among premenopausal women with atypical lesions compared to postmenopausal women with these lesions. We found that the association of

lobular proliferation, fibroadenoma or other BBD with breast cancer was slightly stronger among premenopausal women, although the test for interaction was of borderline significance only for other BBD. We speculate that the increased endogenous hormone levels among premenopausal women may potentiate the risk of breast cancer associated with BBD (40-43). Our results support the notion brought up by previous studies (28,40,44-46) that the early detection and careful follow-up of all types of BBDs among premenopausal women is important in the early detection of breast cancer.

It is important to interpret these results in context of the limitations of this study. Information bias may have lead to misreporting of the types of BBD, since the self-reported information was not verified by review of pathology reports or medical charts. Validation studies have shown agreement between self-reported health data and medical records (7,47-51) and suggest the accuracy of patient self-reports is adequate for use in research studies and quality assurance reports (44,52-55), although there is currently no specific information about the reliability of self-reported BBD. A study by Maunsell and colleagues found that patients had better recall of their invasive tests or procedures when such procedures were performed for reasons other than screening (52). If the same is true of our study population, we would expect to see a higher prevalence of all types of breast disease among cases. However, we did not find breast cysts to be related the risk of breast cancer, suggesting that differential recall is unlikely to be the explanation for the observed associations. Nevertheless, we cannot exclude the possibility of non-differential recall error, particularly regarding lobular proliferation. Because surgery is a major event in a woman's life, recalling disease diagnosis, thus, should be more accurate among women who had surgery than among women who did not. In our study, we found that a self-reported history of surgically treated lobular proliferation was more strongly associated with breast cancer risk than was non-surgically treated disease history. A similar pattern was observed for other BBD. Thus, the risk estimates reported in our study are likely to be underestimated.

This study has several strengths. To our knowledge, this is the first population-based study to investigate the relationship between breast cancer risk and lower categories of BBD among women in China, an area where there is no routine breast cancer-screening program. We have also carefully adjusted for multiple factors related to socioeconomic status and minimized the influence of detection bias. Secondly, the large sample size and extensive exposure information allowed for in-depth evaluation of the BBD and breast cancer risk association. Finally, the use of trained medical professionals and in-person interviews likely minimized the recall bias.

Conclusion

In summary, the results of this population-based, case-control study of breast cancer suggest that low category BBD may be significant contributors to subsequent breast cancer development among middle-aged women, suggesting a need for future research studies to characterize the specific risk. The risk associated with fibroadenoma can be reduced by surgical intervention. Self-reported BBD may be useful tool for early detection of and intervention for breast cancer, in areas where there is no mammography-based breast cancer screening service.

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Appendix I

Categories of the College of American Pathologists classification of benign breast disease (9,10)

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 <i>in situ</i> Lobular carcinoma <i>in situ</i>

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Table 1
Comparison of demographic and breast cancer risk factors between cases and controls by study phase, SBCS (n=6,926)

Characteristics	Phase I [1996-1998]			Phase II [2002-2005]		
	Cases n=1,455 (%)	Controls n=1,556 (%)	P ¹	Cases n=1,997 (%)	Controls n=1,918 (%)	P ¹
Age (yrs, mean ± SD)	47.9±8.0	47.2±8.8	0.03	50.8±8.3	51.6±8.4	0.002
Education						
Elementary/none	12.2	13.9		5.9	11.5	
Junior high school	42.7	41.8		36.6	40.4	
Senior high school	31.5	33.7		41.4	36.6	
Professional/college +	13.6	10.7	0.04	16.1	11.5	<0.0001
Occupational status						
Professional	26.7	24.1		28.6	21.7	
Clerical	22.3	24.1		27.1	26.8	
Worker/farmer	51.0	51.8	0.21	44.3	51.5	<0.0001
Age at menarche (mean ± SD)	14.5 ± 1.6	14.7 ± 1.7	0.0001	14.4±1.7	14.6±1.8	<0.0001
Ever had a live birth	94.9	96.1	0.12	94.9	96.3	0.04
Number of live births (mean ± SD)	1.5±0.8	1.3±0.6	<0.0001	1.2±0.7	1.4±0.8	<0.0001
Age at first live birth, yrs						
<25	28.3	31.6		28.1	32.6	
25-29	51.4	53.4		57.1	54.9	
30-34	16.5	12.4		12.8	10.7	
≥35	3.8	2.6	0.0005	2.0	1.8	-.002
Ever breastfed	77.5	79.2	0.28	72.5	76.1	0.01
Duration of breastfeeding, months (mean ± SD)	11.9±13.3	12.8±14.0	0.09	8.6±9.9	10.7±12.1	<0.0001
Ever had abortion	65.6	66.1	0.768	60.4	62.4	0.02
Menopausal	34.7	36.4	0.34	43.4	49.3	0.21
Age at menopause (mean ± SD)	48.1±4.5	47.4±4.9	0.02	48.5±4.3	48.2±4.6	0.13
Body mass index, kg/m ² (Quartiles: Q ₁ -Q ₄)						
<21.2	22.8	28.2		19.9	22.4	
21.2-23.1	24.2	23.9		23.8	25.5	
23.2-25.3	24.5	23.9		27.1	26.4	
≥25.4	28.5	24.0	0.0003	29.2	25.7	0.004

Characteristics	Phase I [1996-1998]			Phase II [2002-2005]		
	Cases n=1,455 (%)	Controls n=1,556 (%)	<i>p</i> ¹	Cases n=1,997 (%)	Controls n=1,918 (%)	<i>p</i> ¹
Waist to hip ratio (Q ₁ -Q ₄)						
<0.778	25.1	30.9		11.3	20.4	
0.778-0.813	23.3	23.5		20.8	25.8	
0.814-0.850	26.4	25.7		26.0	25.2	
≥0.851	25.2	19.9	<0.0001	41.9	28.6	<0.0001
Exercise participation in preceding 10 years	18.7	25.2	<0.0001	29.2	34.2	0.0009
Ever used oral contraceptives	21.8	22.4	0.61	19.9	20.1	0.88
Ever used any hormone replacement therapy	2.9	2.7	0.52	4.7	3.3	0.03
First degree family history of breast cancer	3.6	2.4	0.05	5.5	3.0	0.0002
Ever had any benign breast disease	35.7	26.3	<0.0001	47.7	33.4	<0.0001

¹ Derived from t-test for continuous variables and chi-square test for categorical variables. Note: Missing data was 0 to 0.5%

Table 2
Characteristics of controls in the case-control study according to BBD² status, SBCS (both phases)

Characteristics	Phase I			Phase II		
	No BBD n=1,147 (73.7%)	Any BBD n=409 (26.3 %)	P ¹	No BBD n=1,278 (66.6%)	Any BBD n=640 (33.4%)	P ¹
Age, yrs (mean ± SD)	47.8±9.1	45.6±7.5	<0.0001	52.3±8.7	50.4±7.5	<0.0001
Education level						
Elementary/none	17.5	3.9		14.8	5.0	
Junior high school	41.7	42.1		40.9	39.5	
Senior high school	31.3	40.3		34.8	40.2	
Professional/college +	9.6	13.7	<0.0001	9.5	15.3	<0.0001
Occupational status						
Professional	22.4	28.9		19.2	26.6	
Clerical	24.2	23.7		26.1	28.3	
Worker/farmer	53.4	47.4	0.03	54.7	45.1	<0.0001
Age at menarche, yrs (mean ± SD)	14.8±1.7	14.5±1.7	0.007	14.6±1.8	14.7±1.8	0.26
Ever had a live birth	95.8	96.8	0.37	95.8	97.2	0.12
Number of live births (mean ± SD)	1.6±0.9	1.3±0.6	<0.0001	1.4±0.9	1.2±0.6	<0.0001
Age at first live birth, yrs						
<25	34.4	23.6		35.7	26.6	
25-29	50.9	60.5		52.4	59.8	
30-34	11.8	14.2		10.2	11.7	
≥35	2.9	1.7	0.0003	1.7	1.9	0.001
Ever breastfed	79.7	77.6	0.37	76.7	75.2	0.75
Duration of breastfeeding, months (mean ± SD)	13.9±15.0	9.5±9.9	<0.0001	11.7±13.2	8.7±9.5	<0.0001
Ever had abortion	66.1	66.4	0.88	60.6	66.1	0.02
Menopausal	40.0	26.2	<0.0001	53.2	41.4	<0.0001
Age at menopause, yrs (mean ± SD)	47.4±4.8	47.5±5.2	0.97	48.2±4.5	48.3±4.9	0.85
Body mass index, kg/m ² (Quartiles: Q ₁ -Q ₄)						
<21.2	26.3	33.7		20.5	25.9	
21.2-23.1	22.6	27.6		23.6	29.2	
23.2-25.3	24.0	23.5		27.1	25.2	

Characteristics	Phase I			Phase II		
	No BBD n=1,147 (73.7%)	Any BBD n=409 (26.3 %)	<i>P</i> ¹	No BBD n=1,278 (66.6%)	Any BBD n=640 (33.4%)	<i>P</i> ¹
Waist to hip ratio (Q ₁ -Q ₄)	21.1	15.2	<0.0001	28.8	19.7	<0.0001
≥25.4						
<0.778	28.7	37.1		19.5	22.2	
0.778-0.813	22.5	26.2		23.9	29.5	
0.814-0.850	26.5	23.5		24.7	26.4	
≥0.851	22.3	13.2	<0.0001	31.9	21.9	<0.0001
Exercise participation in preceding 10 years	26.0	23.0	0.23	35.7	31.2	0.05
Ever used oral contraceptives	21.3	19.8	0.53	21.0	16.1	0.01
Ever used any hormone replacement therapy	2.8	2.4	0.71	5.7	7.8	0.08
Family history of breast cancer	2.4	2.7	0.71	2.0	5.2	0.0001

¹ Derived from t-test for continuous variables and chi-square test for categorical variables

² BBD diagnosed at least 12 months prior to breast cancer diagnosis.

Table 3
Associations between BBD and breast cancer by subtype of BBD, SBCS (both phases)

	All n=6,926 (%)	Case n=3,452 (49.8%)	Control n=3,474 (50.2%)	OR (95% CI) ¹
Without BBD	4,405 (63.6)	1,980 (57.4)	2,425 (69.8)	1.0 Referent
With one type of BBD	2180 (31.5)	1,237 (35.8)	943 (27.1)	1.6 (1.4-1.7)
With ≥2 types of BBD	341 (4.9)	235 (6.8)	106 (3.1)	2.6 (2.0-3.3)
Any BBD				<i>P trend</i> <0.0001
Never	4,405 (63.6)	1,980 (57.4)	2,425 (69.8)	1.0 Referent
Ever	2,521 (36.4)	1,472 (42.6)	1,049 (30.2)	1.7 (1.5-1.8)
Lobular proliferation				
Never	4,869 (70.3)	2,249 (65.2)	2,620 (75.4)	1.0 Referent
Ever:	2,057 (29.7)	1,203 (34.8)	854 (24.6)	1.6 (1.4-1.8)
Age at diagnosis ² , years				
≤38	1,142 (55.5)	677 (56.3)	465 (54.4)	1.7 (1.5-1.9)
>38	915 (44.5)	526 (43.7)	389 (45.6)	1.5 (1.3-1.7)
Years since 1 st diagnosis ³				
≤9	1,066 (51.8)	601 (50.0)	465 (54.5)	1.5 (1.3-1.7)
>9	991 (48.2)	602 (50.0)	389 (45.5)	1.7 (1.5-2.0)
Surgical treatment				
No	1,896 (92.7)	1,104 (92.2)	792 (93.3)	1.6 (1.4-1.8)
Yes	150 (7.3)	93 (7.8)	57 (6.7)	1.8 (1.3-2.5)
Fibroadenoma				
Never	6,404 (92.5)	3,117 (90.3)	3,287 (94.6)	1.0 Referent
Ever :	522 (7.5)	335 (9.7)	187 (5.4)	1.9 (1.6-2.3)
Age at diagnosis, years				
≤35	285 (54.6)	181 (54.0)	104 (55.6)	1.8 (1.4-2.3)
>35	237 (45.4)	154 (46.0)	83 (44.4)	1.9 (1.4-2.5)
Years since 1 st diagnosis				
≤13	258 (49.4)	164 (49.0)	94 (50.3)	1.8 (1.4-2.3)
>13	264 (50.6)	171 (51.0)	93 (49.7)	1.9 (1.5-2.5)
Surgical treatment				

	All n=6,926 (%)	Case n=3,452 (49.8%)	Control n=3,474 (50.2%)	OR (95% CI) ^I
Cystic disease				
Never	89 (17.1)	67 (20.0)	22 (11.8)	3.2 (2.0-5.2)
Ever :	433 (82.7)	268 (80.0)	165 (88.2)	1.7 (1.4-2.1)
Age at diagnosis, years	6,888 (99.5)	3,434 (99.5)	3,454 (99.4)	1.0 Referent
	38 (0.5)	18 (0.5)	20 (0.6)	0.8 (0.5-1.7)
Years since 1 st diagnosis	17 (47.7)	7 (38.9)	10 (50.0)	0.7 (0.3-1.9)
	21 (52.3)	11 (61.1)	10 (50.0)	1.0 (0.5-2.2)
	23 (63.4)	13 (72.2)	10 (50.0)	1.3 (0.6-3.0)
	15 (36.6)	5 (27.8)	10 (50.0)	0.5 (0.2-1.4)
Surgical treatment	12 (31.6)	8 (44.4)	4 (20.0)	1.4 (0.5-4.1)
	26 (68.4)	10 (55.6)	16 (80.0)	0.6 (0.3-1.3)
Other BBD				
Never	6,667 (96.3)	3,290 (95.3)	3,377 (97.2)	1.0 Referent
Ever :	259 (3.7)	162 (4.7)	97 (2.8)	1.6 (1.3-2.1)
Age at diagnosis, years	121 (46.7)	71 (43.8)	50 (51.6)	1.5 (1.0-2.1)
	138 (53.3)	91 (56.2)	47 (48.4)	1.8 (1.2-2.5)
Years since 1 st diagnosis	157 (60.6)	107 (66.0)	50 (51.6)	2.0 (1.4-2.8)
	102 (39.4)	55 (34.0)	47 (47.4)	1.3 (0.8-1.8)
Surgical treatment	100 (39.4)	56 (34.8)	44 (45.8)	1.2 (0.8-1.9)
	157 (60.6)		105 (65.2) 52 (54.2)	1.9 (1.4-2.7)

Note: Missing data <0.5% is not indicated and is excluded from calculation of percentage

^I Adjusted for age (continuous), education, occupation, age at menarche (continuous), age at first live birth (categorized)*, breastfeeding duration in months (categorized), exercise participation in preceding 10 years (yes/no), BMI (categorized), family history of breast cancer (yes/no), oral contraceptive use (ever/never), menopausal status, and study phase (I and II). * Women with no live birth were grouped with those who had 1st live birth at age ≥35.

² Age category is based on the median age for the particular disease in the control population

³ Years since first diagnosis' category is based on the median years for the particular disease in the control population

Table 4
Associations between BBD and breast cancer by menopausal status, SBCS (both phases)

	Pre-menopausal, n=4,042			Post-menopausal, n=2,882			<i>P</i> interaction
	Cases n=1,964 (%)	Controls n=2,078 (%)	OR (95%CI) [/]	Cases n=1,372 (%)	Controls n=1,512 (%)	OR (95% CI) [/]	
BBD							
Never	1,089 (52.4)	1,285 (65.5)	1.0 Referent	891 (64.9)	1,138 (75.4)	1.0 Referent	
Ever	991 (47.6)	677 (34.5)	1.6 (1.4-1.8)	481 (35.1)	372 (24.6)	1.6 (1.3-1.9)	0.59
Lobular proliferation							
Never	1,124 (57.2)	1,490 (71.7)	1.0 Referent	1,017 (74.1)	1,246 (82.4)	1.0 Referent	
Ever	840 (42.8)	588 (28.3)	2.0 (1.5-2.5)	355 (25.9)	266 (17.6)	1.4 (1.2-1.6)	0.81
Fibroadenoma							
Never	1,732 (88.2)	1,959 (94.3)	1.0 Referent	1,272 (92.7)	1,443 (95.4)	1.0 Referent	
Ever	232 (11.8)	119 (5.7)	1.9 (1.4-2.6)	100 (7.3)	69 (4.6)	1.6 (1.2-2.3)	0.44
Cystic disease							
Never	1,952 (99.4)	2,068 (99.5)	1.0 Referent	1,367 (99.6)	1,502 (99.3)	1.0 Referent	
Ever	12 (0.6)	10 (0.5)	1.0 (0.4-2.4)	5 (0.4)	10 (0.7)	0.5 (0.2-1.6)	0.36
Other BBD							
Never	1,998 (96.0)	1,931 (98.3)	1.0 Referent	1,291 (94.1)	1,446 (95.6)	1.0 Referent	
Ever	81 (4.0)	31 (1.7)	2.3 (1.5-3.5)	81 (5.9)	66 (4.4)	1.3 (0.9-1.9)	0.05

[/] Adjusted for age (continuous), education, occupation, age at menarche (continuous), age at first live birth (categorized)^{*}, breastfeeding duration in months (categorized), exercise participation in preceding 10 years (yes/no), BMI (categorized), family history of breast cancer (yes/no), oral contraceptive use (ever/never), age at menopause (categorized) for postmenopausal women only, and study phase.
^{*} Women with no live birth were grouped with those who had 1st live birth at age ≥35.