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A Review Article in:

Histopathological findings in Benign breast lesions

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Abstract

Benign breast lesions are a diverse set of lesions that develop in the mammary epithelium or other mammary tissues and are often associated with vascular, inflammatory, or traumatic pathologies. Some lesions are palpable masses that may be nodular, with specific or nonspecific characteristics. Normal histologic findings range from a preponderance of ducts, lobules, and intralobular and interlobular stroma to patterns of fibrous alteration and cyst formation, once known as fibrocystic disease of the breast. Because this histologic pattern can be seen in up to 50% to 60% of women without breast illness, the term "fibrocystic alterations" is now favored. In this review article, we will review literature about the nature, incidence and the risk of malignant changes in some benign breast lesions.

Introduction

Benign breast lesions are a diverse set of lesions that develop in the mammary epithelium or other mammary tissues and are often associated with vascular, inflammatory, or traumatic pathologies. Some lesions are palpable masses that may be nodular, with specific or nonspecific characteristics, but there are often no specific clinical signs (especially in lesions with greater prognostic significance, such as atypical hyperplasia), and detection is difficult even during diagnostic imaging examinations (1).

Between early adolescence and menopause, the morphologic aspects of the breast alter dramatically. Normal histologic findings range from a preponderance of ducts, lobules, and intralobular and interlobular stroma to patterns of fibrous alteration and cyst formation, once known as fibrocystic disease of the breast. Because this histologic pattern can be seen in up to 50% to 60% of women without breast illness, the term "fibrocystic alterations" is now favored. Women with lumpy breasts or breasts with nondiscrete nodules are not considered to have breast illness, according to

the phrase "fibrocystic alterations." Clinically detectable fibrocystic alterations are not associated with an increased risk of breast cancer (2). The lobules and stroma of the breast may respond to hormonal cues in an excessive manner in women between the ages of puberty and mid-twenties, resulting in the formation of single and multiple palpable fibroadenomas. In autopsy series, 15 to 23 percent of women in this age group were found to have fibroadenomas, whereas specialized clinics discovered 7 to 13 percent and epidemiologic studies found 2.2 percent (3).

The degree of diffuse palpable nodularity may rise in the third and fourth decades of life. This rise is referred to as adenosis in histology, which refers to an increase in the amount of normal lobular tissue. Hypertrophy of the stroma can sometimes occur, resulting in palpable patches of ill-defined fullness, most commonly in the axillary tail. Between the middle of their fourth decade and menopause, glandular tissue may enlarge even more, accompanied by an increase in stromal tissue. Late menopause, hormone replacement therapy, and a thin body composition are all linked to an increased risk of cyst formation (4). Many benign breast lesions have characteristics that make them appear malignant. During the multidisciplinary assessment of these lesions, knowledge of their presentations may help validate radiological pathological concordance of percutaneous biopsy data.

1. Mastalgia (also called mastodynia) is the name given to pain related to the mammary gland occurring either spontaneously or in response to touch, is the common benign lesion and usually resolved spontaneously (5).

2. Fibrocystic changes is the term used to designate a variety of clinical and histopathological changes of the female mammary gland, some of which should be regarded not so much as a disease, more as a

disordering of physiological development, maturation, and involution. In the histological classification by Dupont and Page (1985), fibrocystic changes are divided according to risk into proliferative changes and nonproliferative changes (6). Cystically dilated or ectatic ducts lined by metaplastic apocrine ductal cells having abundant eosinophilic granular cytoplasm. Lumen of the cyst shows eosinophilic secretions and foamy macrophages. Mild epithelial hyperplasia without atypia may be present (7).

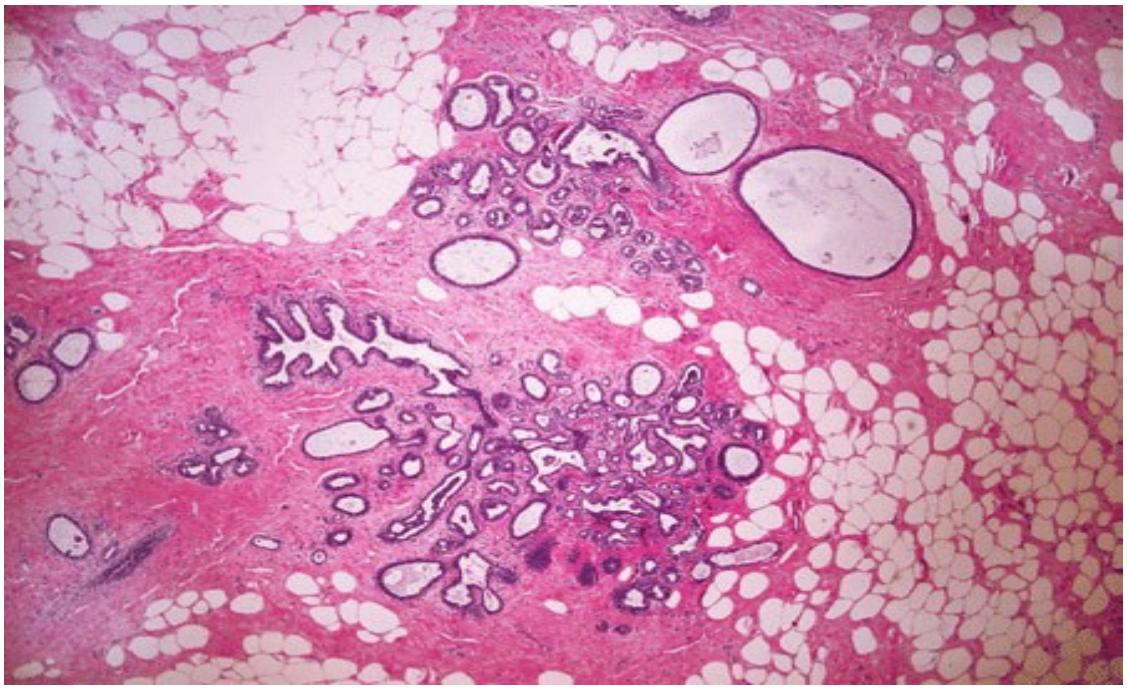

Figure 1. Fibrocystic changes

3. A fibroadenoma is a painless, unilateral, benign (non-cancerous) breast tumor that is a solid, not fluid-filled, lump. It occurs most commonly in women between the age of 14 to 35 years but can be found at any age. Fibroadenomas shrink after menopause, and therefore, are less common in post-menopausal women. Fibroadenomas are often referred to as a breast mouse due to their high mobility. Fibroadenomas is a biphasic tumor, ie, it is composed of an epithelial and a stromal component. The epithelial

component of fibroadenoma can display aberrations similar to those of the epithelial component of the normal breast (8).

Complex fibroadenomas were fibroadenomas harboring one or more of the so-called complex features: epithelial calcifications, apocrine metaplasia, sclerosing adenosis, and cysts larger than 3 mm. At least 0.5 cm of tissue had to be present around the fibroadenoma to evaluate changes in the surrounding breast parenchyma (21).

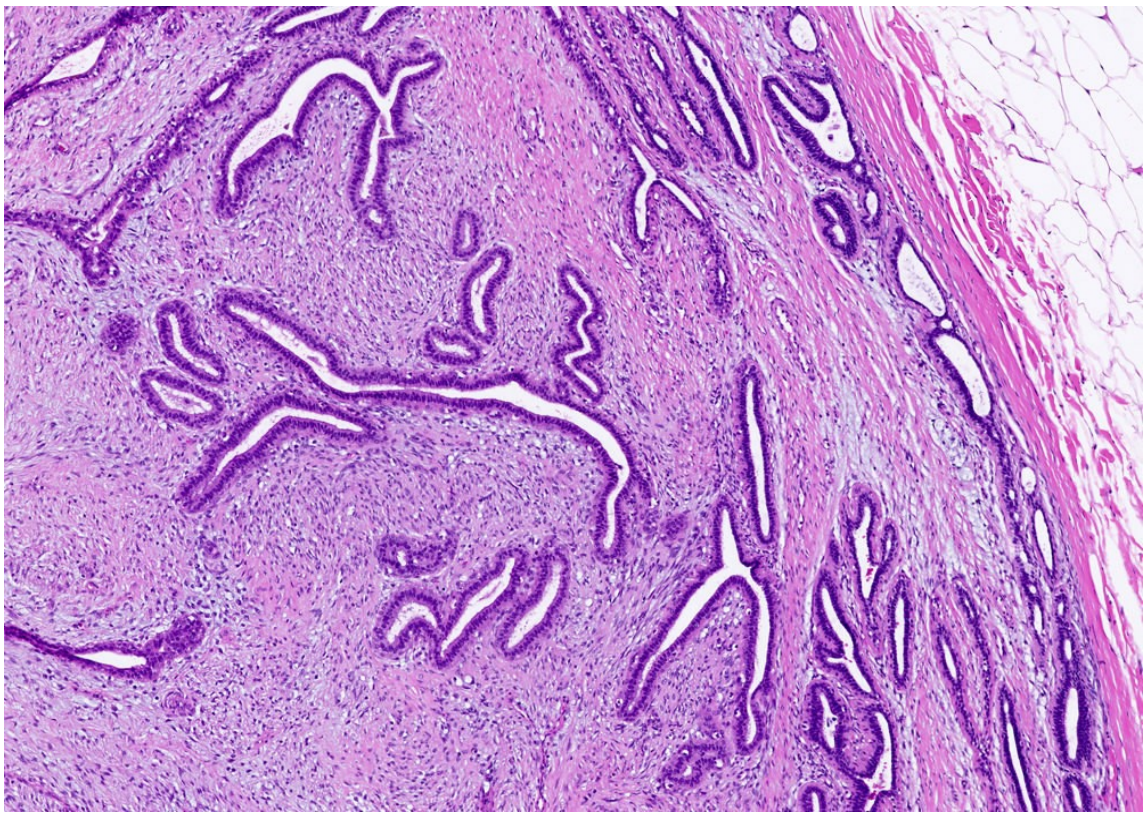

Figure 2. Fibroadenoma in breast tissue

4. Mastitis is a common condition that predominates during the puerperium. Breast abscesses are less common, however when they do develop, delays in specialist referral may occur due to lack of clear protocols. In secondary care abscesses can be diagnosed by ultrasound scan

and in the past the management has been dependent on the receiving surgeon. Acute mastitis accompanied by abscesses is often mistaken for acute inflammatory carcinoma (cancer) of the breasts. In a female child, after birth and during puberty, there may be brief episodes of breast inflammation; these are usually hormone induced and are not caused by bacterial infection. Chronic mastitis is usually a secondary effect of systemic diseases such as tuberculosis, fungal infections, yeast infections, or syphilis. Management options include aspiration under local anesthetic or more invasive incision and drainage (9).

Comparing the frequency of the different types of mastitis the puerperal mastitis is very rare in contrast to the increasing non-puerperal and granulomatous inflammatory breast lesions. The diagnosis "granulomatous mastitis" is one of exclusion. Both non-infectious and infectious causes must be considered. The origin of the granulomatous mastitis often is unknown, but it is supposed to be an autoimmune localized response due to the retained and extravasated fat and protein rich secretions in the ducts in cases of hyperprolactinemia (drug induced or by microprolactinomas) or hormonal imbalances characterized by epitheloid cell granulomas with giant cells microabscesses around lipid drops, but without necroses. An idiopathic type of granulomatous mastitis concerns young women in relationship to parturition with a similar histological pattern predominantly of the lobules. Special types of mastitis are the B-lymphocytic autoimmune mastitis associated with a longstanding insulindependent diabetes mellitus type I, the sarcoidosis, panniculitis and the rare but very different infectious diseases with breast involvement (22).

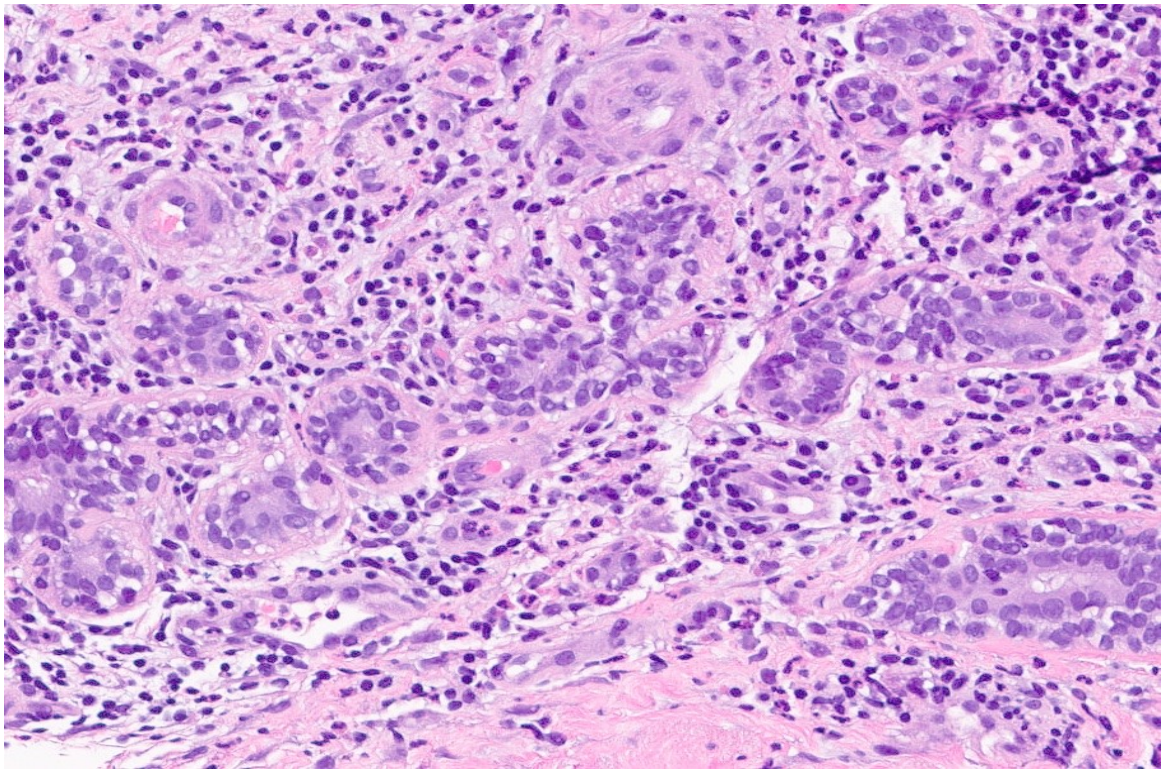

Figure 3. Histological changes in acute mastitis

In this article we will review literature about the above mentioned breast lesions

Review

1. **Mastalgia**

Talimi et al, conducted Surveys showed that more than half of all women report significant breast pain, which in 30% to 40% of cases impairs their everyday and sexual life. In two-thirds of cases, the pain is cyclic and is worst a week premenstrually and perimenstrually. Cyclic mastalgia manifests at around 30 years of age; the onset of noncyclic mastalgia is notably later, at a mean age of 41. What causes mastalgia is unknown. The fact that cyclic mastalgia improves in association with hormonal changes such as when the menopause is reached, and during pregnancy and lactation, suggest a hormonal cause. In a woman with noncyclic mastalgia, inflammatory, neoplastic, and vascular breast disease

needs to be ruled out. In cases with no underlying pathology, rates of spontaneous remission within a few months to up to 3 years are high (6).

Eren et al., found that the Rates of women who had breast fed 3 times or more were higher in the mastalgia group than control group. Increased breast density, and breast imaging-reporting and data system (BI-RADS) 2 mammography findings were related with mastalgia. Cysts and fibroadenomas were more common in the mastalgia group. The incidence of a past history of malignant breast disease was significantly higher in the mastalgia group (8).

Mastalgia is the commonest breast disorder and it is mostly self-limited. The cause is mainly cyclical hormonal changes and also there is non cyclical causes. Mastalgia is associated with fibroadenoma in the study above which mean there may be mutual pathology or there is an effect of cyclical changes on fibroadenoma.

2. Fibrocystic changes

According to Rungruang et al., From the age of 30, about 50% of women develop fibrocystic breast disease, and in 20% of them macrocysts cause symptoms (pain, palpable mass). Sclerosing adenosis is found in 10% to 30% of all women. The pathophysiology of these changes is probably related to an imbalance in the female sex hormones, with predominance of estrogen stimulation and relative progesterone deficiency (10).

Table 1. The most common types of fibrocystic changes and their risk factors.

Lesion type	Histopathological diagnosis	Relative risk of developing breast cancer in the future compared to the risk in the normal population [95% confidence interval]
Nonproliferating	– Simple cysts – Papillary apocrine metaplasia	1.17 [0.94; 1.47]
Proliferating without atypia	– Usual hyperplasia (UDH) – Columnar cell hyperplasia (blunt duct adenosis) – Sclerosing adenosis – Radial scar	1.76 [1.58; 1.95]
Proliferating with atypia	– Flat epithelial atypia (FEA) – Atypical ductal hyperplasia (ADH) – Atypical lobular hyperplasia (ALH)	3.93 [3.24; 4.76]

Tice et al., conducted a study on 42818 women breast biopsies and found that benign breast disease and high breast density independently predict incident breast cancer. Women found on breast biopsy to have atypical hyperplasia and very high breast density had the highest risk for breast cancer. Notably, women with the more common proliferative forms of benign breast disease without atypia were at statistically significantly increased risk for breast cancer in all but the lowest category of breast density, that is, average density, high density, and very high density categories. Women with low breast density, whose breast tissue is almost entirely fat, were at low risk for future breast cancer regardless of the histology of their breast biopsy (11).

Fibrocystic changes is common after age of 30 and its possibly because the hormonal imbalance. The high density of these lesions may be due to histological changes that contribute to malignancy.

3. Fibroadenoma

Khanzada et al., conducted a study on A total of 275 patients during the three years from March 2004 to February 2007 and found that Fibroadenoma was the most common benign breast disease seen in 27% (75/275) of patients, followed by fibrocystic disease seen in about 21% (57/275) patients. Breast abscess was seen in 16% (45/275) patients, duct ectasia in 12% (34/275) and mastalgia in 11% (31/275) patients. Other

benign diseases noted were duct papilloma in 4.7% (13/275), galactocele in 2.5% (7/275), and tuberculous mastitis was seen in 4% (11/275) of patients. About 57% patients with fibroadenoma belonged to 3rd decade of life followed by 32% from 2nd decade of life. About 51% of patients with fibrocystic disease were from 4th decade, 26% from 5th decade and 17.5% from 3rd decade. Breast abscess was commonly seen in patients (58%) of 3rd decade and in 33.3% patients of 4th decade (12).

Table 2. Distribution of benign breast disease (9).

S. No	Disease	Age (in years)					Total
		1-20	21-30	31-40	41-50	51-60	
1	Fibroadenoma	24	43	7	1	-	75
2	Breast Abscess	3	26	15	1	-	45
3	Mastalgia	2	14	11	4	-	31
4	Tuberculosis mastitis	-	6	4	1	-	11
5	Duct Papilloma	-	6	6	-	1	13
6	Galactocele	-	3	4	-	-	7
7	Duct ectasia	-	12	13	9	-	34
8	Fibrocystic diseases	-	10	29	15	3	57
9	Fat Necrosis	-	-	2	-	-	2
	Total	29	120	91	31	4	275

However, Ishtiaq et al.,(13) in their study of 234 patients, found fibrocystic disease as the most common BBD with maximum age incident in the 5th decade of life while Kamal (14) et al found about 65% of patients with fibrocystic disease of breast were from 31–50 years of age where as peak incidence (36%) was between 31-40 years.

In the study of 380 female patients with benign breast diseases that conducted by Kumar et al., 181 (47.63%) had right sided breast involvement while 151 (39.73 %) patients had left breast involvement whereas bilateral involvement was seen in 48(12.63%) patients. In this study Fibroadenoma was more commonly seen in age group of 11 (74.3%) of all cases followed by 29 (18.1%) cases in age group of 31 (6) and

multiple fibroadenoma (3) were more commonly seen in age group. Only one case of fibroadenoma was seen in a one 60 years patient. And figure 1 show the findings of the study (15).

Fibroadenoma id the most common benign tumor in the breast and its mainly after third decade. The hypothesis of it hormonal etiology support the findings our review.

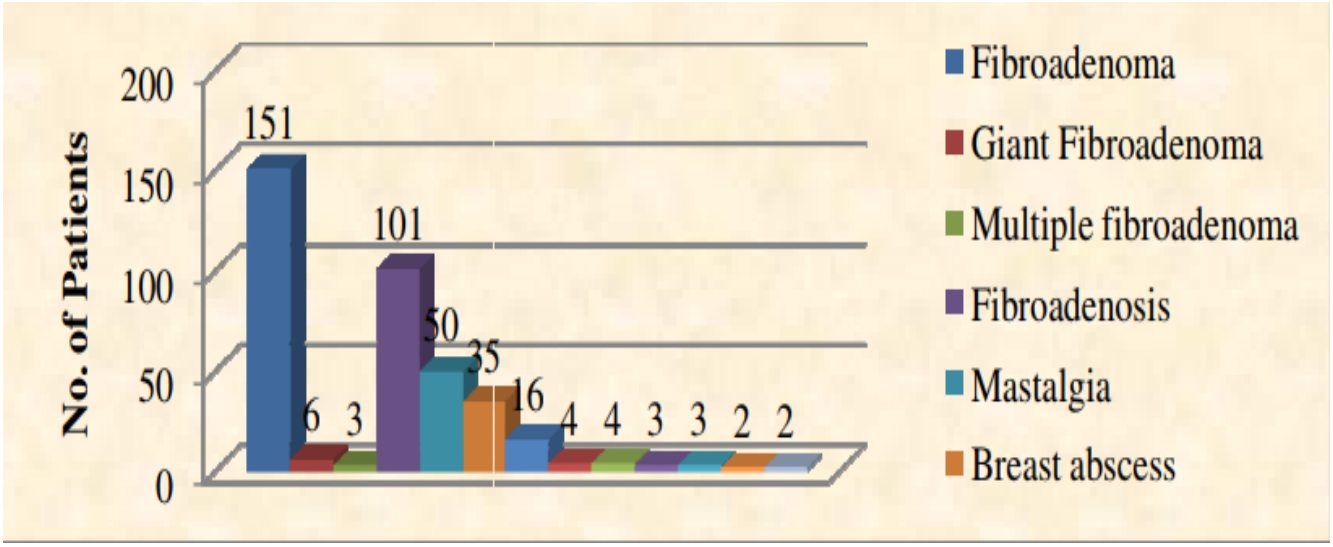

Figure 1

4. Mastitis and abscesses

Mastitis is a complication often encountered in primiparous women and develops in 1% to 24% of breastfeeding women. According to Trop et al., breast abscess develops as a complication of mastitis in 5% to 11% of cases. The most common bacteria is Staphylococcus aureus. Bacteria enter the skin by a small laceration or proliferate in a stagnant lactiferous duct. Common clinical symptoms of breast infection include pain, redness, and heat. Differentiating between mastitis and abscess can be difficult; when there is suspicion for abscess, the woman should be referred for ultrasound evaluation (16).

5. Risk of malignancy changes

Hartmann et al. followed 9087 women for a median of 15 years. The histologic findings they found were nonproliferative lesions in 67 percent of women, proliferative lesions without atypia in 30 percent, and atypical hyperplasia in 4 percent. To date, 707 breast cancers have developed. The relative risk of breast cancer for the cohort was 1.56, and this increased risk persisted for at least 25 years after biopsy. The relative risk associated with atypia was 4.24, as compared with a relative risk of 1.88 for proliferative changes without atypia and of 1.27 for nonproliferative lesions. The strength of the family history of breast cancer, available for 4808 women, was a risk factor that was independent of histologic findings. No increased risk was found among women with no family history and nonproliferative findings. In the first 10 years after the initial biopsy, an excess of cancers occurred in the same breast, especially in women with atypia (17).

Dyrstad et al., in their meta analysis 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 (18).

Schnitt et al., demonstrated that clinical follow-up studies has indicated that there is a relationship between the presence of histologically proven benign breast disease and breast cancer risk and that the level of risk varies according to the histologic category of benign breast disease. In particular, proliferative lesions without atypia are associated with a 1.5- to 2-fold increase in risk, whereas atypical hyperplasias are associated with a fourfold to fivefold increase in breast cancer risk. A number of clinical factors appear to modify the risk associated with these lesions, including

the time since biopsy, menopausal status, and family history of breast cancer (19).

In the study of Kabat et al., the largest cohort study of BBD to date, indicates that women with proliferative breast lesions without atypia have a slightly increased risk of breast cancer, whereas women with atypical hyperplasia have a substantially increased risk. When atypical hyperplasia was examined by histologic subgroup, both atypical ductal and atypical lobular hyperplasia were associated with increased risk, although the estimates of association were imprecise. Our estimates of the risk of breast cancer among women with proliferative lesions without atypia and with proliferative lesions with atypia relative to women with nonproliferative lesions are similar to those of other large cohort studies of BBD (20).

They found no clear association between side of the BBD lesion and side of the subsequent breast cancer. Among women with proliferative disease without atypia and atypical hyperplasia, odds ratios for subsequent breast cancer in the ipsilateral breast were somewhat higher than among those for breast cancer in the contralateral breast, but the CIs were wide and overlapping (20).

The risk for malignant changes is slightly elevated in non proliferative without atypia lesions and highly elevated in the presence of atypia and hyperplasia as the uncontrolled multiplications of the cells is highly contribute in malignancy.

Table 3. Risk of breast cancer according to BBD histology

Histology	No. of cases	No. of controls	Unadjusted odds ratio[a]	95% CI	Adjusted odds ratio[b]	95% CI
Non-proliferative[c]	190	250	1.00	Reference	1.00	Reference
Proliferative without atypia	393	362	1.44	1.11–1.87	1.45	1.10–1.90
Proliferative with atypia	32	12	4.73	2.11–10.61	5.27	2.29–12.15
Atypical ductal hyperplasia	13	6	2.50	0.49–12.87	2.69	0.47–15.61
Atypical lobular hyperplasia	16	5	8.00	1.00–63.96	8.13	0.93–71.12
Atypical columnar hyperplasia	5	1	2.00	0.18–22.05	1.42	0.10–20.70
Columnar cell						
Focal	34	37	0.81	0.47–1.39	0.81	0.46–1.43
Multiple	30	21	1.72	0.87–3.41	1.65	0.81–3.36
Complex fibroadenoma w/o atypia	32	20	1.71	0.94–3.10	1.74	0.94–3.22
Radial scar	13	21	0.53	0.24–1.19	0.58	0.25–1.35
Papilloma						
1–2	56	44	1.13	0.74–1.74	1.09	0.70–1.71
Multiple (≥3)	11	8	1.38	0.56–3.44	1.36	0.52–3.51

Conclusion

1. Fibroadenoma is the most common breast lesion.
2. Mastalgia could be a symptom of many breast disorders.
3. There is a relationship between the type of lesion and age of patient.
4. Although they are benign lesion, there are a potential risk of malignant changes.

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