Original Article

Precancerous Breast Lesions in Benign Breast Lesions: Review of 430 Benign Breast Lesions

Shirish S. Chandanwale, Supreet Kaur, Rahul Nair, Jay Y. Sheth, Sanjyot Nikam, Jehan Nizam Ansari, Manpreet Kaur, Ashily Koshy

Department of Pathology, Dr. D. Y. Patil Medical College, Pune, Maharashtra, India

Abstract

Background: Unanimously recognized precancerous breast lesions are atypical ductal hyperplasia (ADH), atypical lobular hyperplasia, flat epithelial atypia, lobular carcinoma *in situ*, papillary lesions, and proliferative radial scar. The increased risk of developing carcinoma associated with these lesions is found for both ipsi- and contra-lateral breasts. These precancerous lesions are also found in benign breast lesions. **Aim:** The aim of this study is to study histomorphological features of precancerous breast lesions and to find the prevalence of these lesions in various benign breast lesions in different age groups. **Materials and Methods:** We evaluated histomorphology of 430 benign breast lesions for the presence of precancerous breast lesions. The frequency of precancerous lesions was correlated with type of benign breast lesions and different age groups. **Results:** In thirty cases of benign breast lesions, precancerous lesions were found. Maximum cases were of lobular neoplasia (LN) (n = 12) followed by papilloma (n = 9). Majority of the lesions were found between 31 and 40 years (n = 16). Maximum cases of LN (n = 6) and ADH and peripheral papilloma each (n = 4) were seen in the age group of 31–40 years. Maximum precancerous lesions were seen in fibrocystic change (n = 21), followed by sclerosing adenosis (n = 5), and fibroadenoma (n = 4). **Conclusion:** Prevention is a highly feasible approach to breast cancer control. Benign breast lesions with associated precancerous breast lesions must be separated from pure benign breast lesions. These lesions need future evaluations to assess the risk of carcinoma in ipsilateral as well as contralateral breasts. There is a need for more long-term follow-up studies of precancerous breast lesions in benign breast lesions to assess the risk of developing carcinoma in ipsilateral as well as contralateral breasts.

Keywords: *Breast, ductal, hyperplasia, lobular, neoplasia, precancerous*

Introduction

Breast cancer is the second most common type of cancer worldwide, and it remains the most commonly diagnosed malignancy among females.[1] It is one of the leading causes of morbidity and mortality in women. Unanimously recognized precancerous breast lesions are atypical ductal hyperplasia (ADH), atypical lobular hyperplasia, atypical columnar cell hyperplasia or flat epithelial atypia (FEA), lobular carcinoma *in situ*, papillary lesions, and proliferative radial scar.[2,3] These lesions are increasingly found in the screening programs when suspicious areas of breast are core biopsied.[4]

Atypical hyperplasia is a high-risk benign lesion found in approximately 10% of biopsies with benign findings.[5,6] Though atypical lobular hyperplasia and lobular carcinoma *in situ* are widely used for the variable degree of lesions, they do not have prognostic significance. To avoid overtreatment, the term "lobular neoplasia (LN)" is widely used.

The increased risk of developing carcinoma associated with these lesions was found for both ipsi- and contra-lateral breasts. In many studies with long-term follow-up, atypical hyperplasia has been associated with relative risk score for future breast cancer of 4.[7-11] Recent studies suggest that absolute risk among women with atypical hyperplasia has been characterized with a cumulative incidence of breast cancer approaching 30% at 25 years of follow-up.[8,12]

Tamoxifen is approved by the Food and Drug Administration (FDA) for the prevention of breast cancer in women at high risk of developing the disease. It has been further approved for the reduction of contralateral breast cancer.[13-17]

How to cite this article: Chandanwale SS, Kaur S, Nair R, Sheth JY, Nikam S, Ansari JN, *et al.* Precancerous breast lesions in benign breast lesions: Review of 430 benign breast lesions. Clin Cancer Investig J 2017;6:30-4.

Address for correspondence:
Dr. Shirish S. Chandanwale, Dr. D. Y. Patil Medical College, Pimpri, Pune - 411 018, Maharashtra, India.
E-mail: shirishchandanwale@gmail.com

Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_7_17

Quick Response Code:

Detection of these precancerous breast lesions in women with greater risk of developing carcinoma like in those having a family history is of a great importance and will have a possibility of early chemoprevention.[18-20] Radiological findings of precancerous lesions of breast are neither typical nor pathognomonic. Fine-needle aspiration cytology features are inadequate and highly unreliable. They can be assessed with only histological examination.[21]

These precancerous lesions are also found in benign breast lesions. The purpose of this study is to study the histomorphological features of precancerous breast lesions and to find the prevalence of these lesions in various benign breast lesions in different age groups.

Materials and Methods

A total of 430 benign breast lesions in females were included in the study. Inclusion criteria were lumpectomy specimens of benign breast lesions in females diagnosed on clinical, radiological, and or fine-needle aspiration cytology. Exclusion criteria were malignant lesions of the breast and male breast lesions. Clinical findings were noted. The specimens were examined grossly, and multiple sections were taken for histomorphological examination. The sections were formalin fixed and underwent routine paraffin processing. Three to five microns thick sections were cut and stained with hematoxylin and eosin stain. Immunohistochemical (IHC) stains such as cytokeratin (CK) 1/5/10/14, E-cadherin, and estrogen receptor (ER) were in cases of ADH and LN.

Detailed histomorphological features were studied for the presence of associated precancerous lesions such as ADH, LN, FEA papillary lesions, and proliferative radial scar. Histological features in ADH and LN were correlated with IHC findings for definitive diagnosis. The histomorphological features of various precancerous breast lesions associated with benign breast lesions were correlated with various age groups.

Observations and Results

We reviewed histomorphological features of 430 benign breast lesions, out of which 6.97% (n = 30) lesions showed precancerous lesions. Out of 30 lesions, maximum were of LN (n = 12) followed by papilloma (n = 9), ADH (n = 8), and FEA (n = 1). Out of the nine cases of papilloma, maximum were peripheral intraductal papilloma (n = 7) and remaining were central papilloma (n = 2). Maximum lesions (n = 16) were found between 31 and 40 years, followed by 41–50 (n = 11) years, 51–60 (n = 2), and 21–30 (n = 1) years. Table 1 shows detailed frequency of various precancerous breast lesions in different age groups. Out of 16 precancerous lesions in the age group of 31–40 years, the most common lesion was LN (n = 6), followed by ADH and PIP each (n = 4), and all cases of central intraductal papilloma (n = 2).

Majority of the precancerous lesions (n = 21) were seen in fibrocystic change followed by five lesions in sclerosing adenosis and four lesions in fibroadenoma. Out of 21 precancerous breast lesions in fibrocystic change, maximum (n = 10) were LN followed by ADH and papilloma (n = 5) each and one case of FEA [Table 2].

Discussions

Breast cancer remains the most commonly diagnosed malignancy among females.[17] The economic and social impact of this malignancy continues to be enormous. In the recent years, several attempts have been made in understanding the underlying mechanism of cancer development. Models of breast carcinogenesis suggest that atypical hyperplasia occupies a transitional zone between benign and malignant disease. It contains some but not all the requisite features of cancer and thus considered to be premalignant.[22-24] Some drugs are recently approved for the preventive approach of these lesions.[13-16]

Precancerous breast lesions represent a broad spectrum of lesions with a variable risk of progression to carcinoma. Though fine-needle aspiration has been a very important

Table 1: Frequency of various 30 precancerous breast lesions in different age groups

Age group (years)	Flat epithelial atypia	Atypical ductal hyperplasia	Papilloma (central)	Papilloma (peripheral)	Lobular neoplasia
21-30	0	1	0	0	0
31-40	0	4	2	4	6
41-50	1	1	0	3	6
51-60	0	2	0	0	0

Table 2: Distribution of 30 precancerous breast lesions in various benign breast lesions

Benign breast diseases	Flat epithelial atypia	Atypical ductal hyperplasia	Papilloma (central)	Papilloma (peripheral)	Lobular neoplasia	Total/ percentage
Fibroadenoma	0	2	0	1	1	4/13
Fibrocystic changes	1	5	1	4	10	21/70
Sclerosing adenosis	0	1	1	2	1	5/7

diagnostic tool in breast lesions for the past 30 years, it is inadequate and highly unreliable for diagnosing precancerous breast lesions. The diagnosis can only be made by histological examination.[21]

In premammography era, ADH was an incidental finding in benign biopsies. Nowadays, these lesions are most commonly diagnosed in image-guided biopsies taken from the areas of microcalcifications or from the lesions detected by ductal lavage.[18] Lobular carcinoma *in situ* is often found on the occasion of cosmetic surgical procedures and in women with familial risk of breast cancer.[21] Recently, some authors suggested that atypical lobular hyperplasia and lobular carcinoma *in situ* should be designated as LN to avoid overtreatment. The reason for this is that the features which are used to subdivide these lesions are not of prognostic significance.[25]

Benign breast lesions are a heterogeneous group of lesions. Precancerous breast lesions can be seen in benign breast lesions. Out of 430 benign breast lesions, 30 lesions showed associated precancerous lesions. Maximum lesions were LN followed by papilloma, ADH, and FEA. Diagnosis of these lesions was based on histological features assisted by IHC stains.

Out of 12 LN lesions, the ten lesions on histopathology examination showed expansion of acini of one or more lobules by proliferations of small monomorphic cells, less cohesive with uniform round nuclei, and uniform chromatin [Figure 1a]. Two lesions of LN showed larger atypical cells with less uniform chromatin and conspicuous nucleoli [Figure 1b]. IHC staining with E-cadherin was negative [Figure 1c], suggesting a lobular lesion.

Several studies showed that interobserver agreement on the diagnosis of ADH is very poor even when consensus about diagnostic criteria exists.[26] In eight cases of ADH, terminal ductal lobular units (TDLUs) were partially filled with neoplastic proliferation of evenly distributed monomorphic cells with round-to-ovoid nuclei. Distended ducts often show secondary lumina and bridges [Figure 2a]. IHC showed negative staining with CK 1/5/10/14 and positive staining with E-cadherin [Figure 2b], suggesting a ductal lesion. It is known that E-cadherin staining is used to distinguish between lobular and ductal phenotypes.

Percentage of ER-positive cells and intensity of staining are greater in ductal lesions than that of lobular lesions.[12] Similar observations were observed in our study [Figure 3a and b]. Page *et al.* in a landmark longitudinal cohort study in 1985 studied breast cancer risk associated with atypical hyperplasia and found that risk score was 4.4.[10] Other investigators observed relative risk associated with both ADH and lobular hyperplasia to be approximately 4.[7,8,27] More recently, a large cohort study at Mayo Clinic was conducted. They found high cumulative risk of breast cancer among women with atypical hyperplasia.

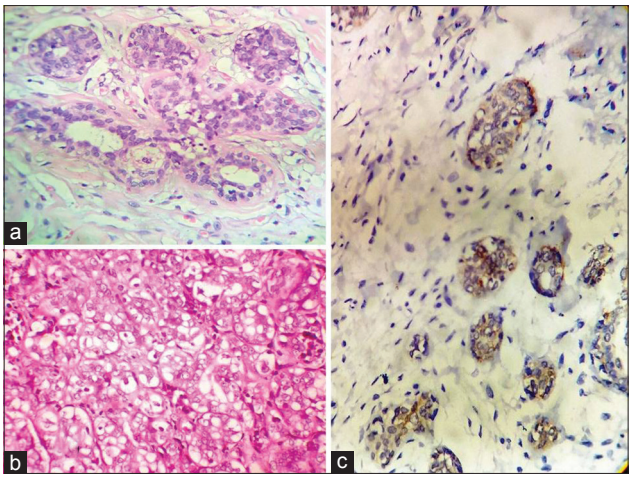

Figure 1: (a) Lobular neoplasia showing monomorphic cells proliferating in the acini of lobules. (b) Acini filled with large pleomorphic cells (H and E, ×400). (c) E-cadherin was negative (immunohistochemistry, ×400)

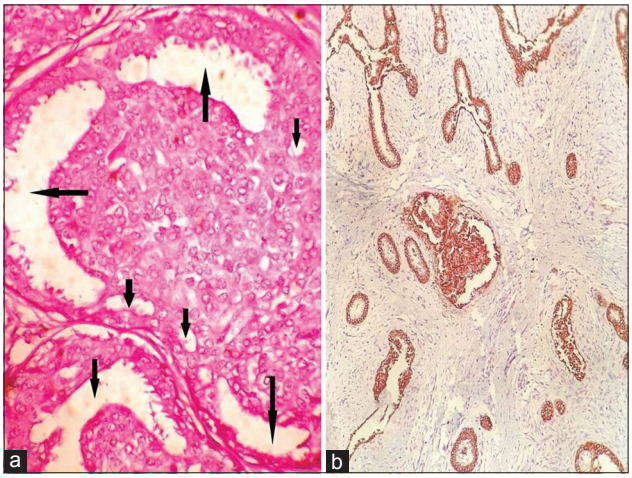

Figure 2: (a) Atypical ductal hyperplasia showing partially filled duct with proliferating cells and with secondary lumens (arrows). (b) Ductal proliferating cells were E-cadherin positive (arrow) (immunohistochemistry, ×100)

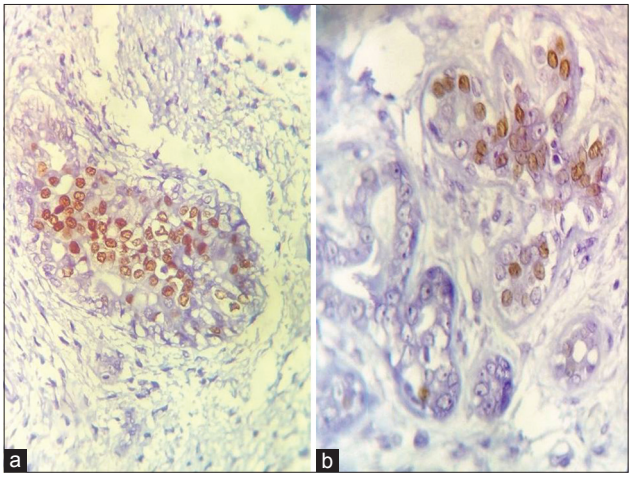

Figure 3: Percentage of estrogen receptor-positive cells in (a) atypical ductal hyperplasia. (b) Lobular neoplasia (immunohistochemistry, ×400)

Specifically 25 years after a biopsy that showed atypical hyperplasia, breast cancer developed in 30% of women.

If atypical hyperplasia is diagnosed in a younger woman, she is more likely to develop breast cancer.[7,8] In our study, out of twenty cases of ADH and LN, 50% (n = 10) were in between 30 and 40 years of age [Table 1]. Maximum cases (n = 15) of ADH and LN were found in fibrocystic change [Table 2].

Fibrocystic change was the most common benign lesion in which associated precancerous lesions (n = 21) were found commonly followed by sclerosing adenosis (n = 5) and fibroadenoma (n = 4). Out of 21 precancerous lesions in fibrocystic change, maximum were of LN (n = 10) followed by ADH (n = 5) and peripheral papilloma (n = 4) [Table 2].

The only case of FEA was seen in fibrocystic change which showed ductal structures lined by one to five layers of mildly atypical cells [Figure 4a].

The relative risk associated with peripheral papilloma may be higher compared to central papilloma.[25] Papillomas were seen in nine benign breast lesions out of which the maximum (n = 7) were of peripheral papilloma which aroused in TDLU [Figure 4b] and two were central papilloma which aroused in larger ducts and were subareolar in location [Figure 4c]. Maximum papillomas (n = 5) were seen in fibrocystic change. The most common age group for papilloma (n = 6) was 31–40 years. Histological diagnosis was made when proliferating epithelial and myoepithelial cells were seen overlying fibromuscular stalk, creating arborescent structure in the ductal lumen. None of the papillomas in our study showed focal atypia.

In benign breast lesions which show associated findings of precancerous lesions, genetic alterations begin to occur quite early. These lesions overexpress estrogen receptor (ER) and transition occurs from normal epithelium to hyperplastic lesions and to carcinoma *in situ*.[28]

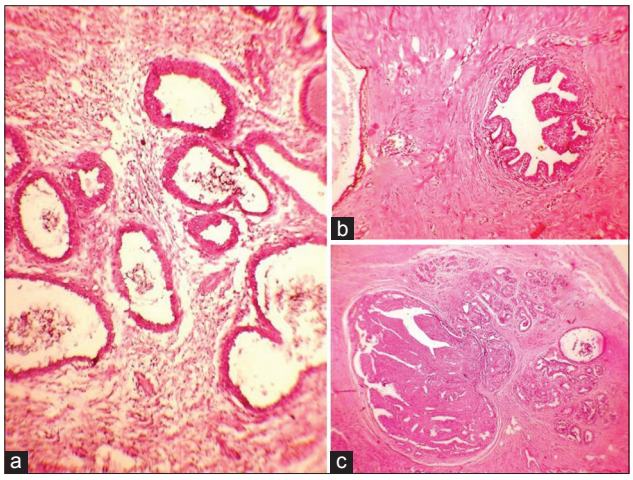

Figure 4: (a) Flat epithelial atypia (H and E, ×400). (b) Peripheral papilloma (H and E, ×100). (c) Central papilloma (H and E, ×400)

Various biomarkers such as ERs, p53, human epidermal growth factor receptor 2-neu, and Ki-67 have been studied to monitor transition. ER status is eventually important in clinical management of patients with premalignant breast lesions.[22]

Use of chemopreventive agents benefits specifically women with atypical hyperplasia. However, a very small minority of high-risk women take drugs despite randomized clinical trials showed substantial benefit specifically for women with atypical hyperplasia.[29] Some drugs are recently approved for the preventive approach of the disease. The most important task is to identify such patients who are likely to get benefited from chemopreventive agents. We did not find any Indian comprehensive follow-up study on precancerous breast lesions.

These precancerous lesions can be multiple in number and they can be present at other sites in the same breast or in contralateral breast. These patients should be followed up and need future evaluations.

Recent studies suggest that surgical excision is not mandatory for atypical lobular hyperplasia if it is an incidental finding. Such cases require careful clinical and radiological follow-up.[30,31] The American Cancer Society recommends annual breast magnetic resonance imaging as an adjunct to mammography for high-risk patients who have lifetime breast cancer risk of approximately 22%–25% or greater.[1]

Current thinking is that prevention is highly a feasible approach to breast cancer control. Several changeable and nonchangeable risk factors such as gender, age, family history, alcohol intake, dietary fat obesity in postmenopausal age, and hormonal stimulation have been attributed to increased cancer risk. Hence, prevention of breast cancer remains strong and intriguing.

Conclusion

Prevention is a highly feasible approach to breast cancer control. Common precancerous breast lesions seen in benign breast lesions are LN, papilloma, ADH, and FEA. Fibrocystic change is the most common disease in which precancerous lesions are seen. The most common age group of these lesions is 31–40 years. Benign breast lesions with associated precancerous breast lesions must be separated from pure benign breast lesions and need future evaluation and follow-up.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153-6.

2. Sewell CW. Pathology of high-risk breast lesions and ductal carcinoma *in situ*. Radiol Clin North Am 2004;42:821-30, v.
3. Jacobs TW, Connolly JL, Schnitt SJ. Nonmalignant lesions in breast core needle biopsies: To excise or not to excise? Am J Surg Pathol 2002;26:1095-110.
4. Ernster VL, Ballard-Barbash R, Barlow WE, Zheng Y, Weaver DL, Cutter G, *et al*. Detection of ductal carcinoma *in situ* in women undergoing screening mammography. J Natl Cancer Inst 2002;94:1546-54.
5. Simpson JF. Update on atypical epithelial hyperplasia and ductal carcinoma *in situ*. Pathology 2009;41:36-9.
6. Gutwein LG, Ang DN, Liu H, Marshall JK, Hochwald SN, Copeland EM, *et al.* Utilization of minimally invasive breast biopsy for the evaluation of suspicious breast lesions. Am J Surg 2011;202:127-32.
7. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, *et al*. Benign breast disease and the risk of breast cancer. N Engl J Med 2005;312:146-51.
8. Hartmann LC, Radisky DC, Frost MH, Santen RJ, Vierkant RA, Benetti LL, *et al.* Understanding the premalignant potential of atypical hyperplasia through its natural history: A longitudinal cohort study. Cancer Prev Res (Phila) 2014;7:211-7.
9. London SJ, Connolly JL, Schnitt SJ, Colditz GA. A prospective study of benign breast disease and the risk of breast cancer. JAMA 1992;267:941-4.
10. Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer 1985;55:2698-708.
11. Degnim AC, Visscher DW, Berman HK, Frost MH, Sellers TA, Vierkant RA, *et al.* Stratification of breast cancer risk in women with atypia: A Mayo cohort study. J Clin Oncol 2007;25:2671-7.
12. Page DL, Schuyler PA, Dupont WD, Jensen RA, Plummer WD Jr., Simpson JF. Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: A retrospective cohort study. Lancet 2003;361:125-9.
13. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 2007;99:283-90.
14. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, *et al.* Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American society of clinical oncology clinical practice guideline focused update. J Clin Oncol 2014;32:2255-69.
15. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, *et al.* Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila) 2010;3:696-706.
16. Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, *et al.* Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 2011;364:2381-91.
17. Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive epidemiology of female breast cancer: An international comparison of screening, incidence, survival and mortality. Cancer Epidemiol 2012;36:237-48.
18. Van de Vijver MJ, Peterse H. The diagnosis and management of pre-invasive breast disease: Pathological diagnosis – Problems with existing classifications. Breast Cancer Res 2003;5:269.
19. Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, *et al.* Prevention of breast cancer with tamoxifen: Preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. Lancet 1998;352:93-7.
20. Veronesi U, Maisonneuve P, Sacchini V, Rotmensz N, Boyle P; Italian Tamoxifen Study Group. Tamoxifen for breast cancer among hysterectomised women. Lancet 2002;359:1122-4.
21. Schreer I, Lüttges J. Precursor lesions of invasive breast cancer. Eur J Radiol 2005;54:62-71.
22. Allred DC, Mohsin SK. Biological features of premalignant disease in the human breast. J Mammary Gland Biol Neoplasia 2000;5:351-64.
23. Santen RJ, Mansel R. Benign breast disorders. N Engl J Med 2005;353:275-85.
24. Bombonati A, Sgroi DC. The molecular pathology of breast cancer progression. J Pathol 2011;223:307-17.
25. Tavassoli FA, Millis RR, Boecker W, Lakhani SR. Lobular neoplasia. In: Tavassoli FA, Devilee P, editors. World Health Organization Classification of Tumors. Tumours of the Breast and Female Genital Organs. Lyon: IARC Press; 2003. p. 60-2.
26. Sloane JP, Amendoeira I, Apostolikas N, Bellocq JP, Bianchi S, Boecker W, *et al.* Consistency achieved by 23 European pathologists from 12 countries in diagnosing breast disease and reporting prognostic features of carcinomas. European Commission Working Group on Breast Screening Pathology. Virchows Arch 1999;434:3-10.
27. Worsham MJ, Abrams J, Raju U, Kapke A, Lu M, Cheng J, *et al.* Breast cancer incidence in a cohort of women with benign breast disease from a multiethnic, primary health care population. Breast J 2007;13:115-21.
28. Stoll BA. Premalignant breast lesions: Role for biological markers in predicting progression to cancer. Eur J Cancer 1999;35:693-7.
29. Waters EA, McNeel TS, Stevens WM, Freedman AN. Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. Breast Cancer Res Treat 2012;134:875-80.
30. Shah-Khan MG, Geiger XJ, Reynolds C, Jakub JW, Deperi ER, Glazebrook KN. Long-term follow-up of lobular neoplasia (atypical lobular hyperplasia/lobular carcinoma *in situ*) diagnosed on core needle biopsy. Ann Surg Oncol 2012;19:3131-8.
31. Murray MP, Luedtke C, Liberman L, Nehhozina T, Akram M, Brogi E. Classic lobular carcinoma *in situ* and atypical lobular hyperplasia at percutaneous breast core biopsy: Outcomes of prospective excision. Cancer 2013;119:1073-9.