



## Histopathologic changes of Non-tumoral Breast Tissue in Patients with Invasive Carcinoma of Breast

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### Abstract

**Background & Aims:** Various studies have shown increased relative risk for breast cancer in patients with different kinds of non-malignant breast diseases. The aim of this study was to evaluate histologic changes in non-tumoral areas of mastectomy specimens of patients with breasts cancer.

**Materials and Methods:** 232 consecutive cases of breast carcinoma were enrolled. Histopathology slides of all 232 cases were evaluated by light microscopy for tumor type, size and grade, lympho-vascular invasion (LVI), perineural invasion and also benign changes of nontumoral breast tissue including hyperplasia, inflammation, atypia, adenosis, sclerosing adenosis, apocrine metaplasia, lactating change, calcification, fibrosis and cyst formation.

**Results:** We found no significant association between nontumoral changes and histologic subtypes of the tumor. Our results showed that in cases with apocrine metaplasia the frequencies of lymph node involvement and lymphovascular invasion were significantly lower than cases without apocrine metaplasia ( $p=0.04$  and  $0.01$ , respectively). Apocrine metaplasia was also associated with tumor grade. It was more frequent in low grade tumors than high grade ones ( $p=0.02$ ). Considering Her2 expression, apocrine metaplasia was seen in only 7% (3/43) of Her2 negative cases in contrast to 29.4% (5/17) in Her2 positive cases ( $p=0.02$ ).

**Conclusion:** It seems that some of the benign nontumoral changes have a probable relationship with breast carcinoma. So we suggest that follow up of the patients with benign breast changes could be useful in preventing or early diagnosis of breast cancer.

**Keywords:** Breast cancer, non-tumor tissue, benign changes

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## Introduction

Breast cancer is the most common malignancy in women and also the second most common cause of cancer related death in women. (1-5) Its incidence varies in different countries and North America and northern Europe have the highest risks for breast cancer. (2,5,6)

Among various risk factors of breast cancer, benign diseases and non-tumoral histologic changes of breast are of great importance. (7-9) Various studies have shown a relative risk of 1.5-1.6 for breast cancer in patients with different kinds of non-malignant breast diseases. (7,10,11) But it is not clear whether benign changes are preceding factors for all or some types of breast carcinomas (10,12) and which types of benign changes are associated with increased risk of breast cancer. (9,12) The aim of this study was to evaluate histologic changes in non-tumoral areas of mastectomy specimens of patients with breasts cancer. The relationship between nontumoral histologic changes and prognostic factors of breast cancer were also studied.

## Materials and Methods

This retrospective study was conducted on 232 consecutive cases of breast carcinoma that had undergone mastectomy in Urmia University of Medical Sciences, Urmia, Iran from March 2016 to March 2017. The research was approved by the Ethics committee of the Urmia University of Medical Sciences and patient consent was obtained from all of the patients.

Histological type of the tumor, tumor size and grade and presence of lympho-vascular invasion (LVI), perineural invasion and also benign changes of nontumoral breast tissue including hyperplasia, inflammation, atypia, adenosis, sclerosing adenosis, apocrine metaplasia, lactating change, calcification, fibrosis and cyst formation were evaluated. Histopathology slides were evaluated by light microscopy.

### Statistical analysis:

The results are expressed as mean  $\pm$  SD. Statistical analysis was performed using SPSS version 16.0.1 (SPSS Inc., Chicago, IL, U.S.A.). The statistical differences between proportions were determined by  $\chi^2$  analysis. Numerical data were evaluated using analysis of variance (ANOVA), followed by Tukey's post hoc test.  $P < 0.05$  was considered as significant.

## Results

The mean age of the patients was  $47.9 \pm 12.1$  years and 22.4% were younger than 40 years old. The most frequent form of breast carcinoma was invasive ductal carcinoma (IDC) (90.9%). Of all 211 invasive breast carcinoma, 28 cases (13.2%) were in grade I, 119 in (55.6%) grade II and 67 cases (31.9%) were in grade III.

Lymph node involvement, LVI and perineural invasion were seen in 163 (70.3%), 132 (56.8%) and 100 (43.1%) cases, respectively.

In evaluation of nontumoral changes, 2 cases showed no histologic change, 17 cases had one type of benign histologic change, 45 cases showed 2 different types of changes, 50 cases showed 3 different changes and 118 cases had more than 3 different types of nontumoral histologic changes. Fibrosis was the most commonly observed nontumoral change (210 cases, 90.5%). Other nontumoral changes are seen in Table 1.

We found no significant association between nontumoral changes and histologic subtypes of the tumor ( $P=0.5$ ). Association between nontumoral changes and tumor histologic properties are in table 2.

Additionally, in cases with apocrine metaplasia, LVI was seen in only 70 (30%) and lymph node involvement in 22 (9.7%) of the cases. Our results showed that in cases with apocrine metaplasia the frequencies of lymph node involvement and lymphovascular invasion were significantly lower than cases without apocrine metaplasia ( $p=0.04$  and  $0.01$ , respectively). Apocrine metaplasia was also associated with tumor grade. It was more frequent in low grade tumors than high grade ones ( $p=0.02$ ).

**Table 1:** Frequency of associated non- tumoral changes in breast carcinoma

Non tumoral change	Hyperplasia			Inflammation			Adenosis	Sclerosing adenosis	Apocrine metaplasia	Lactating change	Calcification	Fibrosis	Cyst formation	Fat necrosis	
	Mild	Moderate	Severe	Atypic	Mild	Moderate									Severe
Number	15	15	4.5	9	111	37	30	17	0	52	43	25	210	165	69
Percent	6.5	6.5	19.4	3.9	47.8	15.9	12.9	7.3	0	22.4	18.5	10.8	9.5	71.1	29.7

**Table 2.** Association of nontumoral changes with prognostic factors of breast cancer

Prognostic Factor	Non- tumoral change	P. value
LVI	apocrine metaplasia	0.01
Lymph node involvement	Apocrine metaplasia	0.04
Tumor grade	Apocrine metaplasia	0.02
Her- 2 expression	Apocrine metaplasia	0.04
Perineural invasion	Severe hyperplasia	0.05
Tumor size	Cyst formation	0.02

## Discussion

In the present study only 2 patients (about 0.9%) had no nontumoral changes. Seventeen cases (7.32%) had only one type of nontumoral changes and 213 patients (91.8%) had more than one type. Wang et al have also reported more than one type of benign histologic changes in most (78%) of their studied cases. (10) Fibrosis was the most frequent change in our study (90.5%), which was very higher than the result of Wang (4.4%) (11).

We found hyperplasia in most of our cases (76.7%), in contrary to Aaman's study (5.1%) (12).

We also found fat necrosis in 29.7% of the cases but it was not reported in most of the cases in the literature (5,6,9-12).

There was no significant relationship between inflammation and histologic subtype of the tumor in our study, but Gulbahce et al, have reported lobulitis in 8%

of the cases with diagnosis of invasive carcinoma ( $p=0.05$ ). (13)

Lee et al have also reported relationship between inflammation and tumor subtype as they have seen intratumoral inflammation more frequently in IDC than invasive lobular carcinoma (ILC) ( $P<0.001$ ). (14)

Cyst formation was seen in 71.1% of our cases, which was different from findings of Wang and Aaman studies (49% and 52.9%, respectively). (11,12) Also, there was significant association between cyst formation and tumors size in our study ( $P=0.02$ ).

In our study, apocrine metaplasia was seen in 22.4% of the cases, comparable with the study of Aaman (30%) but very different from Wang et al report (1.7%). (11,12) We showed that apocrine metaplasia had significant association with tumor grade, absence of LVI, and absence of lymph node involvement ( $P=0.02$ ,  $P=0.01$ ,  $P=0.05$ , respectively).

In the present study, estrogen and progesterone receptors (ER, PR) positivity was frequently seen in grades I and II, but Her-2 expression was mostly seen in grades II and III.(15-16) Similarly, Adedayo found ER and PR positivity in lower grades of the tumor. (17)

No other significant relationship was observed between expression of these ER, PR and Her-2 and other non- tumoral changes.

### Conclusion

According to our findings and regarding the controversial results found in different studies it seems that most benign nontumoral changes have a probable relationship with breast carcinoma. The limitation of our study was relatively small number of cases (only 232 cases), so we recommend extensive studies with higher number of cases to find more reliable results. Additionally, it is not clear that associated nontumoral changes were whether precursors of breast carcinoma or not. Finally it seems that follow up of the patients with benign breast changes as probable risk factors of breast carcinoma could be useful in preventing or early diagnosis of breast cancer.

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### Conflict of interest

The Authors declared that there is no conflict of interest.

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