International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2022; 5(4): 90-94
Received: 13-07-2022
Accepted: 19-08-2022

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Histopathological study of benign proliferative breast lesions in peritumoral area of carcinoma breast - experience in a tertiary care centre

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DOI: https://doi.org/10.33545/pathol.2022.v5.i4b.497

Abstract
Background: Lesions of breast has gained more importance worldwide due to increase in mortality and morbidity associated with breast cancer. In India increase in incidence is due to life style changes and use of hormones. Presence of different proliferative lesions adjacent to malignancy in the same breast proves that carcinogenesis of breast is a multistep process. Women with proliferative breast lesions are more prone to develop carcinoma. Knowledge in carcinogenesis of breast will define the high risk group that improves the screening for carcinoma and management
Aim: The aim is to study the histopathological types of carcinoma breast and benign proliferative breast lesions in peritumoral area.
Materials and Method: This study was a cross-sectional study conducted for a period of 2 years. A total of 85 cases that satisfy the inclusion criteria were included in the present study. Samples were collected in 10% formalin. All the tissue specimens were processed and paraffin embedded. The sections were stained with Hematoxylin and Eosin. Histopathology findings were noted. Results thus obtained was analyzed using SPSS 20.0 version. Statistical analysis was done using Chi square test.
Results: Common age group affected was between 51 to 60 years seen in 30(35.3%) cases. Lesions were predominantly seen in right breast 39 (45.9%). Invasive carcinoma breast No Special Type was the most common malignant lesion (85.9%). Non proliferative breast lesion was common in peritumoral area 46(54.1%). Statistical significance was observed between histopathological diagnosis, tumour size, lymph node status and peritumoral benign proliferative breast lesions.
Conclusion: Proliferative epithelial lesions are at increased risk of subsequent breast cancer. Non proliferative breast diseases are the most common peritumoral lesion in the present study. Even though the risk of transformation to malignancy is less, careful follow-up with clinical breast examination and annual mammographic screening every 6 to 12 months can identify the changes and further it helps to reduce the occurrence of invasive breast cancer.

Keywords: Benign, fibrocystic disease, invasive ductal carcinoma nst, peritumoral area, proliferative breast lesions

Introduction
Carcinoma of breast is a multifactorial disease. Incidence of breast cancer, morbidity, mortality and survival rates vary in different parts of the world. Lesion of breast can be inflammatory, benign and malignant [1]. Carcinogenesis involves a multistep process from hyperplasia, premalignant lesions to carcinoma in situ. According to the risk of developing breast cancer, benign epithelial lesions of breast are classified into non-proliferative breast lesions, proliferative breast lesions without atypia and proliferative breast lesions with atypia [2, 3]. Non-proliferative breast lesions include fibrocystic disease, adenosis, fibroadenoma, duct ectasia and mild hyperplasia. They do not increase the risk of cancer. Proliferative breast disease without atypia includes usual ductal hyperplasia, sclerosing adenosis, intraductal papilloma and complex fibroadenoma. They are associated with 1.5- to 2-fold increased risk of developing breast cancer. Proliferative disease with atypia has moderate increase in risk (4 to 5 fold) of developing subsequent breast cancer. Proliferative lesions with atypia include atypical ductal and lobular hyperplasia [3, 4]. Many studies have been conducted regarding breast lesions and found that risk of developing

breast cancer is associated with proliferative and atypical lesions. Diagnostic methods like mammography, and fine-needle aspiration cytology are being used that helps in preoperative assessment of breast lesions [5]. Benign breast lesions should be distinguished from in situ and invasive carcinomas. This depends mainly on histopathological assessment which helps to recognize the patient's risk of developing carcinomas so that further screening, follow up and proper treatment modality can be initiated [6].

Aims and objectives

Aim of the present study is to assess various types of breast carcinomas and benign proliferative breast lesions in peritumoral area in mastectomy specimens.

The objective of the study is to determine histopathological features of different subtypes of carcinoma breast and correlate with the presence of proliferative lesions of breast in peritumoral area. Multistep process in carcinoma can be proved by the presence of proliferative breast lesions in peritumoral area.

Materials and methods

Observational (Cross sectional) study conducted in Sree Mookambika Institute of Medical Sciences in South India for a period of 2 years from November 2020 to October 2022. Ethical committee approval was obtained. Based on the study conducted by Lekshmi DR *et al.* [7]. Prevalence of carcinoma breast was found to be 53.16%.

p = 53.16%

q = 46.84%

d = 20% absolute error

$Z_{1-\alpha/2}$ = 1.96 for α = 5%

Sample size n = $Z_{1-\alpha/2}^2$ pq / d^2 = 84.62 = 85 cases.

Inclusion Criteria: All mastectomy specimens with proven carcinoma.

Exclusion Criteria: Male patients, trucut biopsy, excision biopsy, post chemotherapy, post-radiotherapy specimens and metastatic tumours.

A total of 85 cases that satisfied the inclusion criteria were included in this study. Specimens were received in 10% Formalin. Clinical details, gross findings including tumor size were noted. Specimen was serially sectioned at 1cm interval. Representative samples from main tumor and peritumoral areas were taken, processed manually and paraffin embedded. Sections were cut and stained with Haemtoxylin and Eosin (H & E).Histopathology findings in main tumor, Modified Scarf Bloom Richardson (MBR) grading, peritumoral area and lymph node metastasis were noted. Data entered in excel sheet. Statistical Analysis was carried out using SPSS version 20.0. Chi square test was done to assess statistical significance. A p value less that 0.05 was considered statistically significant.

Observation and results

Age group of patients included in the study ranges between 35 to 78 years with a mean age of 52 years. Majority of the patients belonged to 51 to 60 years seen in 30(35.3%) cases. (Fig: 1). 35(41.2%) cases belonged to postmenopausal age group, 33(38.8%) and 17(20%) belonged to perimenopausal and premenopausal age group respectively. In the present study, 46(54.1%) of tumors were located at the right side, 39 (45.9%) at the left side breast. None of the patients had bilateral carcinoma.

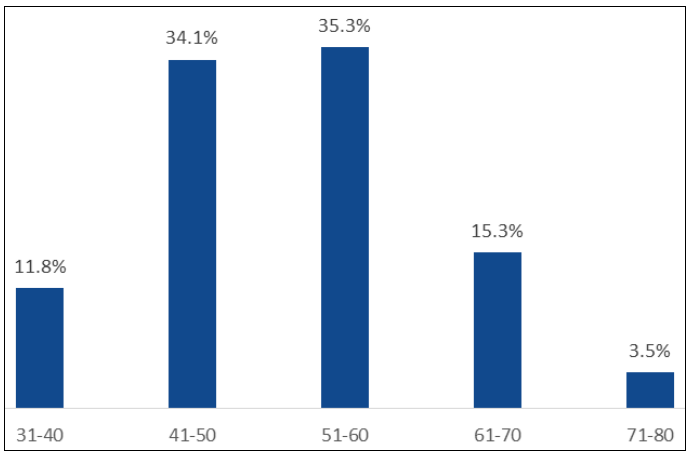

Fig 1: Age Distribution

Of the 85 cases included in the present study 73 (85.9%) were Invasive Ductal Carcinoma of No Special Type (IDC NST). (Table.1)

Table 1: Descriptive analysis of histopathological diagnosis

Histopathology Diagnosis	Frequency	Percent
IDC NST	73	85.9
Tubular Carcinoma	1	1.2
IDC with Sebaceous Differentiation	1	1.2
Invasive Lobular Carcinoma	2	2.4
Metaplastic Carcinoma	3	3.5
Mixed Ductal and Lobular Carcinoma	2	2.4
Mucinous Carcinoma	2	2.4
Encapsulated Papillary Carcinoma	1	1.2

MBR Grading was done to assess histological grade that was based on tubule formation, nuclear pleomorphism and mitotic activity. Grade II lesions were seen in 43(50.6%) which was more common and followed by Grade III lesions in 33(38.8%) and Grade I lesion in 9(10.6%) patients. Out of the 85 cases, 54(63.5%) had tumor size of 2-5 cm, 17(20%) with size more than 5 cm and 14(16.5%) with tumor size less than 2 cm. Maximum cases belonged to T2 group. 28(32.9%) patients had tumor spread to lymph nodes while 57(67.1%) has no lymph nodes metastasis. Most common findings in peritumoral area of breast was non proliferative epithelial lesions 46(54.1%). (Fig 2) Among the non-proliferative lesions, fibrocystic disease was more common.

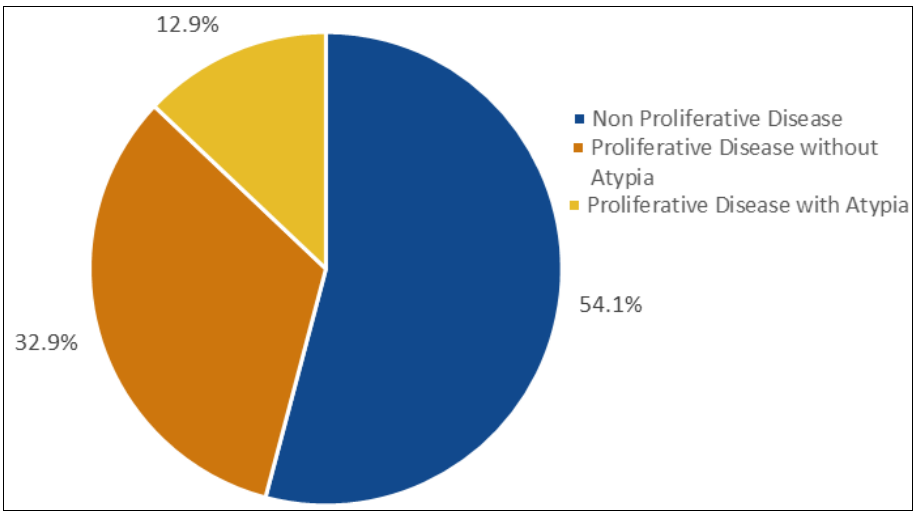

Fig 2: Descriptive analysis of benign proliferative lesions in peritumoral area

Correlation with clinicopathological parameters and benign proliferative lesions in peritumoral area was described in Table 2. Histopathological diagnosis, tumour size and lymph node status were statistically associated with benign proliferative lesions in peritumoral area with a p value of 0.006, 0.08 and 0.01 respectively which is less than 0.05.

Table 2: Comparison of clinicopathological parameters with benign proliferative breast lesions

	Non-Proliferative Disease	Proliferative Disease without Atypia	Proliferative Disease with Atypia	p value
Age				
<50	19	11	7	0.34
>50	27	17	4	
Menopausal status				
Premenopausal (<45)	8	6	3	0.86
Perimenopausal (45-55)	18	10	5	
Postmenopausal (>55)	20	12	3	
Laterality of tumour				
Right	23	15	8	0.39
Left	23	13	3	
Histopathology Diagnosis				
IDC NST	42	25	6	0.006
Others	4	3	5	
MBR Grading				
Grade I	7	1	1	0.17
Grade II	25	15	3	
Grade III	14	12	7	
Tumour size				
<2 cm	11	1	2	0.08
2 - 5cm	29	20	5	
>5 cm	6	7	4	
Lymph node status				
Positive	9	13	6	0.01
Negative	37	15	5	

Discussion

A total of 85 cases were included in the study. Most common age group in the present study was in fourth to sixth decades of life. This was similar to study conducted by Jayker SS *et al.* [8]. In their study, most of cases were seen in the age-group of 41–60 years. Age group of patients in the study was between 35 to 78 years and the mean age group was 52 years. Lekshmi DR *et al.* [7]. Found that carcinoma breast occurrence was highest in the age group of 50 - 80 years with peak incidence in the fifth decade. This was also comparable to study done by Laddha AG *et al.* [9]. Where the age group of patients was between 24 to 77 years. Mean age at diagnosis was found to be 53.33±13.26 years. Divyasree N *et al.* [10]. in their study showed age range of occurrence of carcinoma breast was between 23 to 80 years. The mean age was 51.5 years.

National Surgical Adjuvant Breast and Bowel Project (NSABP) study of women found that the risk of breast cancer was high among postmenopausal women [11]. In the present study 35(41.2%) of carcinoma breast cases were seen in postmenopausal age group. This was comparable to Laddha AG *et al.* [9]. Where 32 (42.67) cases were in postmenopausal age group. Right breast was commonly affected than left side in our study. The finding in the present study was in contrast to study conducted by Agrawal GP *et al.* [12]. Who also observed increased incidence of

breast cancer on left side. Most commonly histological type of breast carcinoma breast was IDC NST 73(85.9%). The finding in the present study was comparable to Jayker SS *et al.* [8] Reddy *et al.* [13]. And Wang *et al.* [14]. In their study observed 93.3%, 85.05% and 90.1% respectively. Divyasree N *et al.* [10]. In their study reported that out of 34 malignant 4(11.76%) cases were medullary carcinomas and one (2.94%) case each of metaplastic carcinoma, invasive papillary carcinoma and apocrine carcinoma. Ayadi L *et al.* [15], reported 8% of invasive lobular carcinoma, 3.2% mucinous carcinoma and 0.6% as metaplastic carcinoma. These findings were comparable to the present study. Present study found that the majority of cases were MBR Grade II category 43(50.6%). Study done by Ayadi L *et al.* [15]. And Ahmed Z *et al.* [16]. Showed similar findings while Divyasree N *et al.* [10]. In their study found predominance of Grade I tumors. Of the 85 cases, 54(63.5%) cases had tumor size of 2-5 cm. This was similar to study done by Munjal *et al.* [17]. in 107 cases, where 71% (76 of 107) had tumor size 2-5cm. Lymph node metastasis was seen in 28(32.9%) cases in the present study. Studies conducted by, Divyasree N *et al.* [10]. Ayadi L *et al.* [15]. And Ahmed Z *et al.* [16]. Also documented lymph nodes metastasis in 51.85%, 41%, and 57.7% respectively.Although non-proliferative disease does not appear to be associated with increased breast cancer risk, proliferative disease without atypia and with atypia (Atypical hyperplasia and sclerosing adenosis) have been associated with a 1.5- to 4-fold increased risk for breast cancer, respectively. It is also valuable in stratifying the risk of carcinoma in contralateral breast [4,8]. Most common benign proliferative lesions in peritumoral area were non proliferative breast disease 46(54.1%). Dupont WD *et al.* [18]. Observed a prevalence of proliferative lesions with atypia, proliferative disease without atypia and non-PD of 4%, 27%, and 69%, respectively. This was comparable to the present study. Hartmann *et al.* [19]. Also showed similar findings with non-proliferative breast lesiosn in 66.6% cases. Among the non-proliferative lesions, fibrocystic disease was more common. The finding in our study was similar to study done by Jayker SS *et al.* [8]. Who found fibrocystic disease in 33% cases? Studies conducted by Shashikala R *et al.* [20]. And Sharma K *et al.* [21]. Also found fibrocystic disease as the most common lesion in peritumoral area that accounts for 38% and 34.78% respectively. Laddha *et al.* [9]. In their study reported proliferative changes with atypia (44%) which was the most common lesion found in peritumoral area of breast neoplasm. They also found that fibrocystic changes and atypical ductal hyperplasia contribute altogether 82.33%. Fibrocystic changes in combination with atypical ductal hyperplasia have a strong synergistic effect in development of breast cancer. Baveja P *et al.* [22]. Showed that intraductal epithelial proliferations were in the form of hyperplasia of usual type (mild or moderate or florid), and ductal carcinoma in-situ adjacent to malignancy which is similar to present study. Sathya lakshmi R *et al.* [23]. Showed usual ductal hyperplasia (60%) that was predominant lesion found adjacent to malignancy in their study. Karpas *et al.* [24]. Reported that there is relative increase in proliferative change in breast with malignant lesions. They stated that there was a relationship between the rare form of fibrocystic disease showing atypical epithelial hyperplasia and cancer. In addition to histologic features of the lesion, the age at biopsy and the degree of family history of breast cancer were reported to be the major determinants of breast cancer risk after the diagnosis of benign breast disease.

Conclusion

Histopathological examination of peritumoral area in mastectomy specimens is a simple and valuable method that helps to stratify the risk of carcinoma in contralateral breast. The present study concludes that non-proliferative breast lesions were the most predominant histological lesion in peritumoral area. Positive correlation was seen with histopathological diagnosis, tumor size, lymph node status and benign proliferative lesions in peritumoral area. Further immunohistochemistry with Ki-67(proliferative marker) to assess the risk of proliferation and transforming into malignancy and p63 (my epithelial marker) to differentiate proliferative lesions with atypia and in situ carcinomas can be done for follow up and management.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest

Acknowledgement
Not available

Author's Contribution
Not available

Conflict of Interest
Not available

Financial Support
Not available

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How to Cite This Article
RN Bejoy, PV Jayasree, SSS Mega, Rajan G. Histopathological study of benign proliferative breast lesions in peritumoral area of carcinoma breast – experience in a tertiary care centre. International Journal of Clinical and Diagnostic Pathology 2022;5(4):90-94.