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A STUDY OF EPITHELIAL CHANGES IN ADJOINING AREAS IN MODIFIED RADICAL MASTECTOMY SPECIMENS IN CASES OF INFILTRATING DUCT CARCINOMA BREAST

KEYWORDS: Benign breast disease, Fibrocystic diseases, Infiltrating duct carcinoma

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ABSTRACT

Aim of the Study: The aims and objectives of our research paper was to detect the incidence of epithelial proliferations in adjoining uninvolved breast in Infiltrating Duct Carcinoma(IDC) cases for which Modified Radical mastectomy was done.

Material and Methods: The study involved analysis of 102 Modified Radical Mastectomy (MRM) specimens of Infiltrating Duct Carcinoma over a period of 18 months

Results: . The epithelial lesions and the tumor were identified based on morphological criteria and tumor was graded as per Nottingham modification of the Bloom Richardson system. Statistical analysis involved Correlation if any between the tumor parameters and epithelial lesions which was determined using Pearsons Chi square test ($p < 0.05$; significant).

Conclusion: It is recommended that extensive random sampling be done from unaffected quadrants which will make surgical pathologists aware of premalignant changes existing and their evolution into breast cancer.

INTRODUCTION:

The term "benign breast diseases" encompasses a heterogeneous group of lesions that begins to rise during the second decade of life and peaks in the fourth and fifth decades. The most common presenting symptoms are breast pain and tender nodularities in breasts. Fibrocystic diseases(FCC) comprise both cysts (macro and micro) and solid lesions including adenosis, epithelial hyperplasia with or without atypia, apocrine metaplasia, radial scar, and papilloma.

FCCs are evaluated under under a classification system first proposed by Dupont and Page [1,2] as nonproliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia (atypical hyperplasia).

Nonproliferative lesions include cysts, papillary apocrine change, epithelial-related calcifications, mild epithelial hyperplasia, as well as ductal ectasia, nonsclerosing adenosis, and periductal fibrosis.

Proliferative lesions without atypia include moderate or florid ductal hyperplasia of the usual type, sclerosing adenosis, radial scar, and intraductal papilloma or papillomatosis. Proliferative lesions with atypia include atypical ductal and lobular hyperplasia.

In each of these lesions the subsequent risk for breast cancer is identified by the histologic appearance of the lesion.

As Wellings et al.showed and Azzopardi [3] strongly emphasized, the site of origin of fibrocystic disease (including that accompanied by the formation of large cysts), so called ductal hyperplasia, epitheliosis or papillomatosis, and most carcinomas (including the ductal type) is the Terminal Duct Lobular Unit(TDLU) and not the large duct system.

Compared with the general population, women with nonpro liferative lesions on breast biopsy have no elevation in breast cancer risk, whereas women with proliferative disease without atypia and women with atypical ductal or lobular hyperplasia have a greater breast cancer risk, with relative risks ranging from 1.3–1.9 and 3.9–13.0, respectively, according to various studies[4].

If a cohort of women undergoing breast biopsies for benign disease are examined, 50% will have proliferative changes. Of these 50%, 5-10% will have atypical hyperplasia. Of this latter category, 15% would develop invasive carcinoma[5].

Materials and Methods:

The study was conducted in the Department of Pathology, Army Hospital (Research & Referral) New Delhi. The study involved analysis of 102 Modified Radical Mastectomy(MRM) specimens of Infiltrating Duct Carcinoma over a period of 18 months.

The Inclusion Criteria for our study were all cases of Infiltrating Duct Carcinoma for which Modified Radical Mastectomy was conducted at the Oncosurgery centre of our hospital.

All cases who had received chemotherapy prior to surgery were excluded.

After the gross evaluation of the specimen the entire breast specimen was cut longitudinally into slices appoximately 2 cm thick with one cut at the level of the nipple.

Three sections from the tumor and at least one section from each uninvolved quadrant in the following order (Upper outer, lower outer, lower inner, upper inner quadrant and post areolar) was taken. All lesions noted grossly or radiologically were sampled. Sections from the nipple and areola along with surgical margins as per standard procedures employed were taken.

Standard five micron thick paraffin embedded Hematoxylin and Eosin(H&E) stained sections were examined. The epithelial lesions and the tumor were identified based on morphological criteria and tumor was graded as per Nottingham modification of the Bloom Richardson system.

Statistical Analysis:

Statistical analysis involved Correlation if any between the the tumor parameters and epithelial lesions which was determined using Pearsons Chi square test ($p < 0.05$; significant).

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Result:
The study consisted of 102 cases of infiltrating duct carcinoma who underwent MRM (no preoperative chemotherapy) at a tertiary care hospital.

The majority of cases, were in age group above 60yrs(36.2 %), 49 (48.03%) cases were in age group 41-60yrs, 04 cases were below 30yrs(2.9%). In this study the youngest patient was 28yrs and oldest 82yrs. The Mean Age was 54.87 (± 13.75). All cases were women.

In analyzing the cases age 55yr was deemed to give sharpest dividing line between those in the premenopausal and those in postmenopausal states. There were 59 cases of breast cancer in patients less than 55yrs of age, youngest being 28yrs of age and 43 cases of breast cancer in patients 55yrs or older, the oldest being 82yrs.

There was a preponderance of carcinoma on the left side of breast (55.88%) as compared to right side of breast (53.9%).

Statistically the upper outer quadrant had a significantly higher incidence of tumor involvement compared to the other three quadrants in both groups, however the p value done by Pearson Chi Square test was 0.441 which was not significant [Table1].

Table 1: Quadrant location based on Menopausal Status

QUADRANT	PREMENOPAUSAL (=<55YRS)	POSTMENOPAUSAL (>55YRS)	TOTAL
OUTER UPPER	26(44.1%)	15(34.9)	41(40.2%)
INNER UPPER	14(23.7%)	15(34.9%)	29(28.4%)
OUTER LOWER	06(10.2%)	03(7%)	09(8.8%)
INNER LOWER	05(8.5%)	06(14%)	11(10.8%)
SUBAREOLAR	05(8.5%)	04(9.3%)	09(8.8%)
>1 QUADRANT	03(5.1%)	0(0%)	03(2.9%)
	59(100%)	43(100%)	102(100%)

The number of lymph nodes excised ranged from 12-30, the average being 18 nodes per axilla. Among 59 cases younger than 55yrs of age there were 35 patients with nodal metastasis (59.32%). Among 43 who were 55yrs or older, there were 25 patients with lymph node metastasis(58.13%)[Table2].

Table 2: Nodal Metastasis in Both Groups

AGE GROUP(YRS)	NO LN METASTASIS	LN METASTASIS	%
<55	24	35	59.32
>55	18	25	58.13

The random sections were taken from 4 quadrants and retroareolar area in MRM specimens of IDC and were studied for benign breast disease which encompass the broad spectrum of histopathological lesions. The microscopic distribution of benign breast lesions, regardless of the type was uniformly dispersed throughout all quadrants in majority of cancerous breasts. In only 5 out of 59 patients less than 55yrs of age with cancer did the cancer bearing quadrant contain the most marked degree of proliferative lesions including DCIS/ADH as opposed to the other three quadrants. In patients 55yrs of age and older no differences were noted in the cancer bearing quadrant as opposed to the other quadrant.

Comparative study of the incidence of Benign Breast Diseases-Non Proliferative lesions(NP), Proliferative lesions without atypia (PDWA) [Figure1A], Hyperplasia of usual type(HUT)[Figure1B], Atypical Ductal Hyperplasia(ADH)[Figure1C] and Ductal carcinoma in situ (DCIS)[Figure1D] in premenopausal (<55yrs) and postmenopausal (>55yrs) was conducted [Table3].

Figure1: Photomicrograph showing (a) Atypical ductal hyperplasia;(b) sclerosing adenosis;(c) DCIS-comedo necrosis type;(d) hyperplasia of usual type (H& E, ×100)

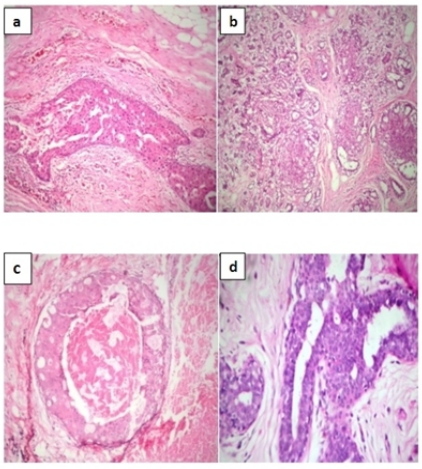

Table 3: Distribution of cases according to the benign epithelial activity

BPED	<55YRS (N=59)	>55YRS(N=43)
NP	18(30.5%)	13(30.2%)
PDWA	44(74.57%)	33(76.7%)
HUT	50(84.74)	34(79.06%)
ADH/DCIS	26+21(79.6%)	18+18(83.7%)

Of the patients less than 55yrs of age, 50 (84.74%) showed hyperplasia of usual type and 47 (79.6%) showed marked atypical epithelial hyperplasia and ductal carcinoma in situ. Of those who were 55yrs of age or older 34 (79.06%) showed hyperplasia of usual type and 36(83.7%) showed marked atypical ductal hyperplasia and DCIS.

Thus both premenopausal and postmenopausal groups with invasive carcinoma were found to have a high incidence of ADH/DCIS in four quadrant evaluation.

The presence of BBD either occurring singly or multiple lesions in four quadrants of breast was studied[Table 4].

Table 4: Correlation between multiplicity of BBD with breast cancer

BPED	ALL CASES	PERCENTAGE
NP=1	02	1.96%
NP>1	02	1.96%
P=1/P>1,NO ADH	32	31.3%
NP+P/P>1 + ADH	44	43.13%
NP or P+DCIS	22	21.56%
TOTAL	102	

Our study depicted 98 patients (nearly 96%) of our study group had more than one benign breast disease. Women with multiple proliferative lesions with ADH comprised 43.13% of all cases. Those with single or multiple proliferative lesions without ADH constituted 31.3% of the cases.

BBD was also correlated with various histological tumor parameters like the size of tumor, the Lymph node metastatic status and histopathological grade of tumor[Table 5].

Table 5.Correlation of BBD with tumor characteristics

	CASES	ADH	DCIS
TUMOR SIZE			
<2cm	11	03(30%)	01(10%)
2-4.9cm	83	38(45.7%)	31(37.3%)
>5cm	08	04(44.4%)	07(77.7%)
NODAL STATUS			
0	43	14(32.5%)	08(18.6%)

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1-3	42	23(58.9%)	16(41.02%)
>4	17	07(35%)	11(55%)
GRADE			
I	10	02(20%)	01(10%)
II	31	13(41.9%)	10(32.2%)
III	61	29(47.5%	26(42.6%)

There was no statistical significance found between tumor size and nodal status with ADH (the p value was 0.441 and 0.16 respectively), however there was significant statistical correlation between tumor size and nodal involvement with DCIS (p value was 0.002 and 0.001) respectively.

Discussion:

Benign breast disease is an important risk factor for breast cancer. An understanding of the relationship between the pathologic characteristics of breast cancers and the type and multiplicity of BBD in various quadrants could provide important information about the development of breast cancer [6,7]. A linear stepwise progression of breast tumorigenesis has been postulated, from usual ductal hyperplasia through atypical hyperplasia, ductal carcinoma in situ(DCIS), and invasive carcinoma, analogous to the sequence of events in the development of colon cancer[8,9].

We studied multiple sections from the four quadrants and retroareolar region of breasts removed in cases of Infiltrating Duct Carcinoma, in an attempt to detect the patterns of epithelial proliferations in the adjoining uninvolved breast and correlate them with tumor, histological and clinical parameters.

The results of the study show benign breast diseases in most quadrants to be frequently coexistent with carcinoma.

In our study 59(57.8%) cases were <55yrs and 43(42.15%) were above 55yrs of age.

In this study the youngest patient was 28yrs and oldest 82yrs.

In their series of 1000 cases of breast cancer, Fisher et al [10] found an incidence of 19.5% in the age group 20-44yrs, 23.9% in the age group 45-54yrs and 55.6% above 55yrs of age.

In a study done at National Cancer Institute, Bethesda during 2000-2004, the median age at the time of breast cancer diagnosis was 61 years [11]. The median age in our study was 52 years.

In our study, there was a slight preponderance of left sided carcinoma as compared to right side(55.88%% and 44.12 % respectively).These findings are consistent with those of Fisher et al [10] whose study also had a slight left sided preponderance (51.4% and 48.6% respectively).

The location of cancer according to quadrants in patients younger than 55yrs and in those 55yrs and older in our study was similar to the distribution in series of Tellum et al[12].Most studies have shown the upper outer quadrant has a greater risk of cancer than the other quadrants[13,14]. This may probably be due to the association of the upper outer quadrant with the axillary tail which is a channel for drainage of lymph to the axillary lymph nodes and may carry micro-metastasis more than the other quadrants of the breast.

The association of the more severe atypical changes with cancer in both pre and post menopausal group tend to confirm the conclusions reached by Humphrey et al., that large duct atypical hyperplasia are an important feature in the development of breast cancer [15].

His conclusions were based on a follow-up of patients who showed such hyperplastic changes associated with cystic disease and subsequently had a relatively increased incidence of breast carcinoma.

In our cross sectional study we found 98 patients (nearly 96%) of our study group had more than one benign breast disease. Women with multiple proliferative lesions with ADH comprised 43.13% of all cases. Those with single or multiple proliferative lesions without ADH constituted 31.3% of all the cases.

Prospective studies done by Maria J.Worshametal et al [16] have shown that multiple non proliferative or proliferative BBD lesions with or without atypia are significant predictors of risk of progression of BBD to breast cancer.

In our study BBD were correlated with various histological tumor parameters.i.e size of the tumor, lymph node metastatic status and histopathological grade of tumor. We found that there was increase in the tumor size and grade in patients having high grade proliferative lesions, and high statistical significance was found between tumor size, nodal metastasis and DCIS only. This was in concordance with the study of Tellum et al who correlated the incidence of nodal metastasis with proliferative lesions with atypia However in a retrospective study done by R. Arisio et al [17], 1075 patients with invasive breast carcinoma and with known nodal status were analysed. Interestingly, the association with in situ carcinoma was correlated with lower nodal positivity in tumors presenting equally sized infiltrating components.

Aside from the morphologic intcrrelationship of cancer and benign disease of the breast, one may theorize that those stimuli producing benign proliferative disease are also cancer development, and therefore benign cystic and proliferative disease reflect a milieu in which cancer has a greater propensity to arise. This brings up the consideration of the endocrine environment or the sensitivity of the breast to this environment.

Estrogen is known to be etiologically important in the development of breast cancer; estrogen effect on target organs is mediated through its receptor, and in the case of breast epithelium, it appears that estrogen effect includes the induction of proliferation, particularly of ductal tissue and therefore leads to increased predilection of breast cancer [18].

Conclusion:

A four quadrant study of 102 radical mastectomy specimens has been presented and studied for various BBD associated with IDC.

During grossing section taking from unaffected areas is generally ignored. It is recommended that extensive random sampling be done from these unaffected quadrants which will make surgical pathologists aware of premalignant changes existing and their evolution into breast cancer.

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