

## COMPARATIVE ANALYSIS OF ESTROGEN, PROGESTERONE, C-ERBB-2 RECEPTOR STATUS OF AGE MATCHED MALE AND FEMALE BREAST CARCINOMA

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### ABSTRACT

**Objective:** To assess the estrogen receptor (ER), progesterone receptor (PR) status and Her-2/neu oncogene mutation in male breast carcinomas and to compare these prognostic markers with age matched female patients.

**Methodology:** This is a comparative descriptive study carried out in the department of Pathology (Histopathology), Army Medical College, Rawalpindi, with necessary collaboration with Armed Forces Institute of Pathology (AFIP), from January 2007 to January 2009. Twenty male patients were divided in different age groups and age group matched 20 female breast carcinoma cases were selected. Request forms and haematoxylin and eosin (H & E) stained slides were assessed for age of the patients, type and grade of the tumor. Tumors were graded according to the Nottingham Modification of Bloom-Richardson classification and Immunohistochemical scoring for ER and PR was done by H Scoring method. The *c-erbB-2* scoring was done according to DAKO Scoring system.

**Results:** Forty (20 males and 20 females) patients of breast carcinoma were included in the study. Majority were having invasive ductal carcinoma. The predominant histological grade was grade-II. Statistically significant correlation, was found between the intensities of ER and PR in male patients as compared to female patients ( $p$  value =0.001) except in age group 26-35 where it was more in females ( $p$  value =0.001). There was no significant difference in the *c-erbB-2* scoring of both groups ( $p$  value >0.05).

**Conclusion:** Male breast cancers display distinct immunophenotypic features than in females, implying a different pathogenesis in the evolution and progression of this disease. This recognition may provide better-focused treatment strategies and improved survival.

**KEY WORDS:** Male breast carcinoma, ER, PR status, *c-erbB-2*.

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## INTRODUCTION

Breast carcinoma is the commonest malignant tumor and the leading cause of cancer death in women, with more than one million new cases occurring worldwide annually.<sup>1</sup> It accounts for 22% of all female cancers in Pakistan.<sup>2</sup> In comparison to female breast carcinoma, carcinoma of the male breast (MBC) is a rare disease and

in western literature it is reported as less than 1% of all breast cancers,<sup>3</sup> with an estimated number of 1500 new cases per year world wide.<sup>4</sup>

Overall, the epidemiology of MBC presents similarities with the epidemiology of female breast cancer (FBC). Major genetic factors associated with an increased risk of breast cancer for men include BRCA2 mutations, which are believed to account for the majority of inherited breast cancer in men. Epidemiologic risk factors for MBC include disorders relating to hormonal imbalances such as obesity, testicular disorders and radiation exposure.<sup>5</sup>

Prognosis and management of breast cancer in both males and females are influenced by the classic variables such as age of the patient, histological type and grade, tumour size, lymph node status, status of hormonal receptors—Estrogen Receptor (ER) and Progesterone Receptor (PR) and *c-erbB-2* status.<sup>6</sup> Data from more than 2,000 male patients in the Surveillance, Epidemiology, and End Results (SEER) cancer registry show that 93.7% of male breast cancers are ductal or unclassified carcinomas, 2.6% are papillary, 1.8% are mucinous and only 1.5% are lobular.<sup>7</sup>

Breast cancers are traditionally stratified into hormone receptor-positive and negative groups to guide patient management. This is because almost all hormone antagonist (ie, tamoxifen) - responsive breast cancers are estrogen receptor (ER) and/or progesterone receptor (PR) -positive. These cancers are associated with a lower rate of cell proliferation and well differentiated tumours, leading to a better prospect of overall survival.<sup>8</sup> Recent evidence also supports a role for *c-erbB-2* status of breast cancers as predictive of their sensitivity or resistance to various forms of systemic therapy. Most recently, *c-erbB-2* protein expression has been used to select patients for treatment with monoclonal antibody to the *c-erbB-2* protein. Furthermore, some clinical studies have suggested that *c-erbB-2* over-expression is predictive of resistance to tamoxifen.<sup>9</sup>

The aim of this study was to assess the estrogen receptor (ER), progesterone receptor (PR)

status and *c-erbB-2* oncogene mutation in male breast carcinomas and to compare these prognostic markers with age matched female patients.

## METHODOLOGY

Study was carried out from January 2007 to January 2009 at department of Pathology (Histopathology), Army Medical College. Twenty male patients were divided in different age groups and age group matched 20 female breast carcinoma cases were selected. The patients' age, type and grade of the tumors were recorded from original request forms and haematoxylin and eosin (H & E) stained slides.

Tumors were graded according to the Nottingham Modification of Bloom-Richardson classification.<sup>10</sup> Immunohistochemical scoring for ER and PR was done by H Scoring method.<sup>11</sup> The *c-erbB-2* scoring was done according to DAKO Scoring system.<sup>12</sup> No staining at all, or membrane staining in <10% of the observed tumor cells was considered negative (0). A faint/barely perceptible membrane staining in >10% of tumor cells or staining of part of their membrane was scored as negative (1+). A weak to moderate staining of the entire membrane in >10% of the tumor cells was considered weakly positive (2+). A moderate to strong staining of the entire membrane in >10% of the tumor cells was scored as strongly positive (3+). Sections from female breast carcinomas with known immunoreactivity for all antigens were used as positive controls.

The data was fed in computer program SPSS version 15 for windows and correlation of staining of ER, PR and *cerbB2* between males and female groups was calculated by using Spearman correlation. Results were compared between groups by using Chi Square Test. Results were considered significant with *p* value less than 0.05.

## RESULTS

Forty (20 males and 20 females) patients of breast carcinoma were included in the study. The patients were split into four different age groups. In female group 19 (95%) cases were of

Table-I: Comparison of ER, PR Score of breast tumors in female and male patients (n = 20)

Age Groups	ER Score & Status different cases Females	PR Score & Status different cases Females	ER Score & Status different cases Males	PR Score & Status different cases Males	Chi Square Test (X <sup>2</sup> )	Degree of Freedom	Probability Value (p value)
26-35years	200(Strong), 100(Moderate) 140(Moderate)	100(Mild), 90(Mild) 110 (Moderate)	60(Mild), 80(Mild) 140 (Moderate)	70(Mild), 45(Negative) 210(Strong)	ER=332 PR=105	3	0.0001
36-45 years	30(Negative), 190(Moderate) 140(Mild), 60(Mild)	10(Negative), 180(Moderate), 80(Mild), 80(Mild)	240(Strong), 235(Strong), 225(Strong), 230(Strong)	210(Strong), 235(Strong), 240(Strong), 210(Strong)	ER=355 PR=395	33	0.0001 0.0001
46-55 years	20(Negative), 10(Negative) 210(Strong), 90(Mild) 200(Strong)	30(Negative), 10(Negative) 240(Strong), 10(Negative) 100(Mild)	225(Strong), 280(Strong) 235(Strong), 140(Moderate) 235(Strong)	240(Strong), 245(Strong), 245(Strong), 125(Moderate) 240(Strong)	ER=476 PR=597	44	0.0001 0.0001
56-65 years	180(Mild), 160(Mild) 140(Mild), 120(Moderate) 220(Strong), 210(Strong) 120(Moderate), 210(Strong)	130(Mild), 120(Mild) 110(Mild), 210(Strong) 170(Moderate), 140(Moderate) 210(Strong), 240(Strong)	295(Strong), 255(Strong) 40(Negative), 260(Strong) 160(Moderate), 245(Strong) 44(Negative), 200(Moderate)	300(Strong), 270(Strong), 70(Mild), 260(Strong) 210(Strong), 240(Strong) 55(Mild), 230(Strong)	ER=565 PR=699	77	0.0001 0.0001

infiltrating ductal carcinoma and one (5%) case was of invasive lobular carcinoma. Among male patients, all 20(100%) cases were of invasive ductal carcinoma. The predominant histological grade was grade-II.

Of 20 cases of females, 17 (85%) cases were ER positive and 3 (15%) cases were negative. Among the ER positive cases, strong positivity was seen in 6 (30%) cases, moderate positivity in nine (45%) cases and mild positivity in two (10%) cases. Among progesterone receptors, 16 (80%) cases were PR positive and four (20%) cases were progesterone receptor negative. Strong positivity was found in four (20%) cases, moderate positivity in eight (40%) cases and mild positivity in four (20%) cases. Seventeen (85%) cases were *c-erbB-2* positive and three (15%) were negative (1+). Of all *c-erbB-2* positive cases, 12 (60%) cases showed strong positivity (3+), 5 (25%) cases showed weak positivity (2+).

The breast tumors in male patients showed 18 (90%) cases as estrogen receptor positive and two (10%) cases as estrogen receptor negative. Twelve (60%) cases showed strong positivity, four (20%) showed moderate positivity and two (10%) showed mild positivity. Progesterone receptor positive cases were found to be 19 (95%) and only one case was PR negative. Strong positivity for PR was seen in 15 (75%) cases, moderate positivity in one (5%) case and mild positivity was seen in three (15%) cases. A total of 19 (95%) cases were found to be *c-erbB-2* positive. Only one (5%) was *c-erbB-2* negative. Eighteen (90%) cases were strongly positive (3+) for *c-erbB-2* and one (5%) was weakly positive (2+).

The overall correlation of ER and PR scores in males and females patients of different ages are presented in Table-I and Table-II respectively. Significant statistical correlation (Table-I) was found between the intensities of ER and PR in male patients as compared to female pa-

Table-II: Comparison of c erb B2 Score of breast tumors in female and male patients (n = 40)

Age Groups	Female Patients		Male Patients		Chi Square Test (X <sup>2</sup> )	Degree of Freedom	Probability Value (p value)
	C erb B2 Score and Status in different cases	C erb B2 Score and Status in different cases	C erb B2 Score and Status in different cases	C erb B2 Score and Status in different cases			
26-35years	3+(Strong), 3+(Strong)	3+(Strong), 3+(Strong), 2+(Mild/Moderate)	3+(Strong), 3+(Strong), 1+(Negative)		1.0	2	0.607
36-45years	2+(Mild/Moderate)	2+(Mild/Moderate)	3+(Strong)	2+(Mild/Moderate)	0.333	3	0.954
46-55years	3+(Strong), 3+(Strong)	3+(Strong), 3+(Strong)	3+(Strong), 3+(Strong)	3+(Strong), 3+(Strong)	—	4	0.513
56-65years	1+(Negative), 3+(Strong), 2+(Mild/Moderate), 3+(Strong), 2+(Mild/Moderate), 3+(Strong)	3+(Strong), 3+(Strong), 2+(Mild/Moderate), 3+(Strong), 3+(Strong)	3+(Strong), 3+(Strong), 3+(Strong), 3+(Strong)	3+(Strong), 3+(Strong)	2.0	7	0.960

tients in all age groups ( $p$  value =0.001), except in age group 26-35 where it was more in females ( $p$  value =0.001). There was no significant difference in the *c-erbB-2* scoring of both groups ( $p$  value >0.05) (Table-II).

## DISCUSSION

In this study the predominant histological type was infiltrating ductal carcinoma in both males and female patients as is observed in most of the studies throughout the world.<sup>4</sup>

Regarding hormone receptor studies have reported higher percentage of hormonal receptor positivity in male breast carcinoma (80%-95% higher),<sup>13,14</sup> than in female breast cancers and same was found in the present study. In women hormone receptors are well characterized, and ER expression is usually a marker of differentiation and indicates that the cancer still remains under hormonal influence. Positive expressions of ERs and PRs correlate with better survival and response to estrogen antagonists such as tamoxifen.<sup>15</sup> Contrary to this studies have shown that in men, ER-positive tumors are

associated with higher stage disease. In ER + and PR + tumors, overall survival in males is inferior than in females.<sup>16</sup> However, in one study the aggressiveness was found to be equal.<sup>17</sup>

The percentage of *c-erbB-2* over-expressing tumor immunopositivity in males was similar to that found in most of the females in this series, but in another study *c-erbB-2* over-expression was found to be more in males than female breast carcinoma with a worse outcome when compared stage for stage. These conflicting results may be due in part to different scoring systems and cut-off values used.<sup>18</sup>

Although male breast carcinoma is a relatively rare form of malignancy, it appears that further studies of *c-erbB-2* gene and hormone protein status in male breast carcinoma are warranted to determine whether their hormone receptors and oncogene has clinical utility for the management of patients with this disease.

## CONCLUSIONS

Few studies have addressed the differences between male breast carcinoma and female

breast cancer. More research is needed on male breast cancer as it becomes more apparent that it is a different disease than its female counterpart. Male breast cancers display distinct immunophenotypic features from those occurring in women, implying a different pathogenesis in the evolution and progression of this disease. This recognition will provide better-focused treatment strategies and improved survival, and will perhaps even provide us with a better understanding of breast carcinogenesis both in men and women.

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