

# Status of ER, PR, HER-2 and E-cadherin Expression in 86 Female Breast Cancer Patients from Bangladesh

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## ABSTRACT

**Background and objectives:** Breast carcinoma of female is a leading cause of morbidity and mortality. Till date, a lot of studies have been carried out to find the accurate prognostic parameters of breast carcinoma to facilitate its treatment. In Asian population frequency of reactivity of some of these parameters like estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER-2) and E-cadherin receptor differs from the western population. As no more data are available on Bangladeshi population, this study was designed to find out the status of these receptors for this specific ethnic group.

**Materials and methods:** Total 86 histopathologically confirmed samples of breast carcinoma were included in this study. Histologically, they were divided into lobular and nonlobular category. Immunostain was done for ER, PR, HER-2 and E-cadherin receptor study. Statistical analysis was done to find out the association of these receptors with histological classification and grade.

**Results:** The mean age of the patients was  $45.6 \pm 10.7$  years. Among histological subtype, total 9 (10.5%) found to be of lobular category and 77 (89.5%) were nonlobular type. Out of 86 patients, almost two third (61.6%) of patients were ER positive and 54.7% were PR positive. On the other hand 24 (27.9%) patients showed HER-2 overexpression and 79.1% patient showed E-cadherin positivity. About 64 (83.1%) nonlobular carcinoma was positive for E-cadherin. Only E-cadherin receptor showed significant association with histological classification.

**Conclusion:** It has been found that Bangladeshi population has lower rate of ER positivity when compared with the Western population and there is significant association between the histological type of breast carcinoma and E-cadherin receptor positivity.

**Keywords:** Breast cancer, E-cadherin, Estrogen receptors, Human epidermal growth factor receptor 2, Progesterone receptors.

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## INTRODUCTION

Female breast cancer is still considered as one of the major causes of morbidity and mortality in the world.<sup>1,2</sup> It is one of the most common malignancy among females.<sup>3</sup> Although it is the most frequent cancer among Bangladeshi females, there are no more epidemiological data available on the literature regarding this ethnic group.<sup>4</sup> According to the National Institute of Cancer Research and Hospital registry data of Bangladesh about 30% of female cancers of the country is breast cancer.<sup>5</sup>

There are many traditional morphological prognostic factors in breast cancer including histological type, tumor size, tumor grade, and axillary lymph node metastasis.<sup>6</sup> Aside from that hormonal receptor status, ploidy and proliferating markers are also taken into account.<sup>7</sup> Pathologists use immunohistochemistry for characterizing intracellular proteins or various cell surface proteins which are also useful for prognostication of tumors. Recently, more importance has been given to the biological molecular prognostic factors, because a significant number of patients with early-stage breast cancer is having microscopic metastasis at the time of diagnosis.<sup>6</sup> Though there are numerous prognostic indicators which are currently under use or under investigation, till date it is impossible to predict the outcome of a breast cancer patient accurately. For this reason, there is continuous search for refined and better biological markers of prognosis and more effective treatment modalities.

Some of the human breast cancers are known to be hormone dependent.<sup>8</sup> Differentiation and proliferation of breast epithelial cells is regulated by estrogen as they interact with the ER in the nucleus. One of the most important risk factor for breast cancer is prolonged exposure of estrogen. ER also regulates PR expression in normal breast epithelium.<sup>9</sup> On the other hand, HER-2 receptor

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represents amplification of HER-2 gene. This receptor normally controls cell growth. Overexpression of HER-2 receptor is related with poor prognosis of the disease.<sup>10</sup> Analysis of ER, PR and HER-2 receptor status is now accepted as established procedures for the management of patients with breast cancer.<sup>11</sup> On the other hand, E-cadherin is considered as a calcium regulated adhesion molecule which is expressed in most of the epithelial tissues of the body.<sup>12</sup> Chromosome *16q22.i* is the location for cadherin gene.<sup>13</sup> E-cadherin is associated with formation of glands, epithelial polarization and stratification.<sup>14</sup> It has been observed that, E-cadherin mutation affects the extracellular domain which is responsible for alteration of cell shape and interference with cell adhesion. Poorly differentiated tumors commonly presents with loss of E-cadherin. Mutation of

E-cadherin is associated with metastasis.<sup>13</sup> Detection of status of E-cadherin expression can help with prediction of aggressiveness of the breast cancer.<sup>15</sup> Prediction of aggressiveness of the tumor can guide the aggressive treatment protocol, thereby increasing the chances of survival.<sup>16</sup>

The present study was done to find out the ER, PR, HER-2 and E-cadherin receptor status of 86 Bangladeshi breast cancer patients and its association with histological subtype and grade.

## MATERIALS AND METHODS

This cross-sectional study was carried out at the Department of Pathology at a tertiary care center in Dhaka, Bangladesh. Data were collected during the period of July 2015 to June 2017. Total 86 specimens of modified radical mastectomy were taken through purposive and convenient sampling. Patient's relevant history was recorded in a predesigned data sheet after taking informed written consent from them. Samples from the patients who were on neo-adjuvant therapy were not included in the study. Ethical clearance for this study was obtained from the Institutional Ethical Committee.

After receiving, the samples were grossed and processed for routine histopathology reporting with hematoxylin and eosin staining. Samples were broadly classified into lobular and non-lobular carcinoma and were graded using Nottingham modification of the Bloom–Richardson system.

For immunohistochemistry staining, 4  $\mu$ m thick tissue sections containing the tumor tissue as well as adjacent normal epithelium were taken on poly-L-lysine coated slide from the paraffin blocks of tumor. After epitope retrieval, the tissue was treated with a polymer based detection system (Envision plus, Dako, Carpinteria, CA) using mouse monoclonal antibodies for ER and PR (Dako, Carpinteria, CA). For HER-2, herceptin kit (Hercep test, Dako, Carpinteria, CA) were used as per the manufacturer's instructions. Reporting of ER, PR and HER-2 was done according to College of American Pathologist Guideline 2013. Equivocal cases of HER-2 were not included in the study as further investigation with fluorescent *in situ* hybridization

(FISH) could not be arranged. For E-cadherin FLEX monoclonal mouse anti-human E-cadherin clone NCH-38 ready to use (LINK) was used as primary antibody and DAKO REAL™ EnVision™ (HRP RABBIT/MOUSE) (ENV) were used as secondary antibody.

Immunostaining for ER, PR and HER-2 and E-cadherin was done at Armed Forces Institute of Pathology (AFIP), Bangladesh, Dhaka and immunostaining expression was evaluated based on the intensity of immunohistochemical expression and was classified semiquantitatively.

## RESULTS

Age range of the study patients was 27–77 years with a mean age of  $45.6 \pm 10.7$  years. Total 31 patients belonged to 41–50 years age group which constitute the highest frequency.

Among histological subtype, total 9 (10.5%) found to be of lobular category and 77 (89.5%) were nonlobular type. Out of the 86 patients almost two third (61.6%) of patients were ER positive and 38.4% of patients were ER negative. PR positivity was found in 54.7% patients and was negative in 45.3% patients. On the other hand 24 (27.9%) patients showed HER-2 over expression and 62 (72.1%) patients showed of HER-2 negativity.

About 79.1% patient was E-cadherin positive. E-cadherin was more positive in nonlobular carcinoma (83.1%) than lobular carcinoma (44.4%). Association between histological subtype (lobular and nonlobular) and their ER, PR, HER-2 and E-cadherin receptor status are presented in Table 1. None of the group showed significant association except E-cadherin which showed significant association with histologic subtypes.

Almost three fourth (72.1%) of patient's tumor were moderately differentiated (grade II), 20 (23.3%) were poorly differentiated (grade III) and 4 (4.6%) patient's tumor were well differentiated (grade I). Association between E-cadherin expression and histopathology grade was done and presented in Table 2. Tumor grades and E-cadherin expression did not show any significant association.

**Table 1:** Association between receptor status and histologic subtype of tumor

Receptor status		Lobular (n = 9)		Nonlobular (n = 77)		p value
		n	%	n	%	
ER	Positive	6	66.7	47	61.0	1.00
	Negative	3	33.3	30	39.0	
PR	Positive	6	66.7	41	53.2	0.50
	Negative	3	33.3	36	46.8	
HER-2	Positive	3	33.3	21	27.3	0.70
	Negative	6	66.7	56	72.7	
E-cadherin	Positive	4	44.4	64	83.1	0.017*
	Negative	5	55.6	13	16.9	

\*p < 0.05

**Table 2:** Association between histologic grade and E-cadherin expression of tumor

Tumor grade	E-cadherin				p value
	Positive (n = 81)		Negative (n = 5)		
	n	%	n	%	
Grade I	4	4.9	0	0.0	0.358
Grade II	57	70.4	5	100.0	
Grade III	20	24.7	0	0.0	

## DISCUSSION

Age distribution of the patients in the present study showed that, more than one third (36.0%) of patients' age belonged to 41–50 years age group. The mean age was  $45.6 \pm 10.7$  years, ranging from 27 to 77 years. Almost similar mean age was observed among the breast cancer patients from Iran, Turkey and Egypt. The mean age of these studies were  $51.5 \pm 11.8$  years, 50 years and  $52.67 \pm 8.19$ , respectively.<sup>17–19</sup>

It has been found in other study that commonly the mean incidence of ER and PR positivity is around 77–55%, respectively.<sup>20</sup> But in the present study about 61.6% patients were ER positive and 54.7% were PR positive. This difference is not unusual as previous studies showed that ER positivity among the Indian population is lower than the western population and the frequency of ER negativity is higher in Indian population (46.5%) than in west (10%).<sup>21</sup> This differences could be due to diagnosis of the breast cancer at late stage in our population in comparison with the western population. In regards to HER-2 over expression, current study shows 27.9% positivity which is almost similar with other study on Indian population showing 29.46% positivity.<sup>22</sup>

No significant association was found in current study when ER, PR and HER-2 positivity were plotted against two major subtypes of breast carcinoma (lobular and nonlobular carcinoma). Similar finding is also reported by Wong et al.<sup>23</sup> This study population includes patients of early-stage invasive lobular carcinoma and invasive ductal carcinoma of patients' cohorts from two differing nationality and ethnicity namely Australia and Hong Kong. So it can be concluded that though there is difference between the frequencies of ER and PR positivity among Indian and western population, there is no differences among them in respect to association between receptor positivity and major tumor subtypes.

In respect to E-cadherin expression, current study showed 83.1% positivity in nonlobular carcinoma which is a bit higher than a study carried out in Saudi Arabia where the positivity was 72%.<sup>16</sup> Lower rates (55%) of E-cadherin positivity was found in a study from USA.<sup>24</sup> This differences may be due to different ethnicity of the cohort and also may be due to small number of sample size in all these three studies. Current study showed that there is significant association of E-cadherin expression with histologic subtype of breast cancer. Similar finding was also noted by Acs et al. ( $p \leq 0.001$ ).<sup>25</sup>

The present study investigated the association between tumor grade and E-cadherin expression. But no association between E-cadherin expression and tumor grade could be established. Similar finding was also reported by Gamallo et al.<sup>26</sup> Although it is known that loss of E-cadherin protein is related with invasive and metastatic potential of neoplastic cells it might not be an important factor that influence tumor grade.

## CONCLUSION

It can be concluded that, our population have lower rate of ER positivity than the western population while the frequency of expression of E-cadherin remains similar with other ethnic groups. Although E-cadherin expression showed significant association between lobular and nonlobular variant it is recommended that further study with large number of study population should be conducted for future reference.

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