Correlation between E-Cadherin and Hormone Receptor Status among Breast Cancer Patients

Anusha Hassan Ali, Ghulam Haider, Khalil Ahmed, Madiha Hashmi, Perwasha Kerio and Razia Irshad

Department of Medical Oncology, Jinnah Postgraduate Medical Centre, Karachi, Pakistan

ABSTRACT

Objective: To determine the association between E-cadherin expression and hormone receptors status in patients with breast cancer.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Medical Oncology, Jinnah Postgraduate Medical Centre, Karachi, Pakistan, from March to December 2019.

Methodology: Two hundred and forty-eight women, aged 18-65 years with histologically proven diagnosis of breast carcinoma, were included in the study. Immunohistochemistry (IHC) staining was performed for the evaluation of E-Cadherin expression and status of hormonal receptors [Estrogen receptor (ER), Progesterone receptor (PR) and HER-2-neu]. The positive homogeneous pattern of staining for the cellular membranes is considered normal. The non-homogeneous or the heterogeneous pattern of the cytoplasm and membrane, represented aberrant E-cadherin expression (loss of E-cadherin expression). SPSS version 23 was used to analyse data.

Results: The results of IHC showed that 82.7% of the tumours were E-cadherin positive, 65.7% were ER positive, 62.9% were PR positive and 29.4% were HER 2 positive. A normal pattern of immunostaining of E-cadherin for the membranes is seen in hormone receptor positive and young patients with low grade tumour. Aberrant E-cadherin expression (loss of E-Cadherin) was noticed in HER 2 negative, postmenopausal women with high grade large size tumour ($p < 0.05$).

Conclusion: The study showed that there is significant association between E-cadherin expression and hormone receptor status, HER2-neu, menopausal status, age of patients, grade of tumour and size of tumour.

Key Words: E-cadherin, Hormone receptors, Breast carcinoma, ER, PR and HER 2.

How to cite this article: Ali AH, Haider G, Ahmed K, Hashmi M, Kerio P, Irshad R. Correlation between E-Cadherin and Hormone Receptor Status among Breast Cancer Patients. *J Coll Physicians Surg Pak* 2020; **30(10)**:1030-1034.

INTRODUCTION

E-cadherin is a protein that is present in the epithelial tissues of breast. It is encoded by CDH1 gene. It is significant in maintaining adhesion between cells of epithelium and responsible for transition between mesenchyme and epithelium. It possesses tumour suppressing properties. Loss of E-cadherin may result in invasion and distant metastasis.^{1,2} Breast cancer is ranked as second most common cancer globally; and reported as 25% of all the cancers.³ Despite availability of wide variety of treatments like chemotherapy, surgery, radiotherapy, endocrine therapy, targeted therapy and immunotherapy, breast cancer prognosis and treatment still seem to be very challenging.⁴ Pakistan is ranked highest among Asian countries in breast cancer incidence.⁵

E-cadherin loss is mainly coupled with non-cohesive and invasive pattern in invasive carcinoma of breast. It is still ineffectively comprehended that E-cadherin loss is associated with phenotype of invasive lobular carcinoma. There is an ongoing debate regarding loss of E-cadherin, including the deactivation of CDH1, which is typically the loss of heterozygosity on chromosome 16q, transcriptional deactivation and homozygous erasure.⁶ E-cadherin is a kind of cell bond glycoprotein. It not only inhibits invading of cancerous cells, but also metastasis.⁷ It is a typical inhibitor of cell development. When epithelial-mesenchymal progress happens in malignant cells, E-cadherin diminishes or shows malfunction, consequently causing diminished loss of extremity and invasion of the encompassing tissue development and cell bond. It might spread to different organs of the body like liver, bone, lung or brain.⁸

There are different investigations that are used to confirm breast cancer (histological type, grade of tumour, lymph node status, tumour size, human epidermal growth factor receptor-2 (HER-2), estrogen receptor (ER), and progesterone receptor (PR)).⁹ Even with multiple investigations, the prognosis remains vague and is not able to predict the survival of patients with breast cancer.¹⁰

Therefore, it is crucial to explore new parameters that help predict survival of breast cancer patients. The down regulation of

Correspondence to: Dr. Anusha Hassan Ali, Department of Medical Oncology, Jinnah Postgraduate Medical Centre, Karachi, Pakistan
E-mail: hakroali@gmail.com

Received: June 15, 2020; Revised: September 22, 2020;

Accepted: October 17, 2020

DOI: <https://doi.org/10.29271/jcpsp.2020.10.1030>

E-cadherin is reported to be associated with poor outcomes in breast cancer patients and hence survival rate is not higher.¹¹ Therefore, it is very imperative to determine the role of E-cadherin among breast cancer patients. Nonetheless, the correlation of E-cadherin with hormone receptor status is still of great value. Hence, the aim of this study was to evaluate the association between E-cadherin and hormone receptor status.

METHODOLOGY

It was a cross-sectional survey conducted at the Department of Medical Oncology, Jinnah Postgraduate Medical Centre, Karachi, Pakistan, from March to December 2019. Sample size of 248 patients with breast cancer was estimated using open EPI-online sample size calculator by taking statistics for the positive expression rate of E-cadherin as 36.44% in invasive ductal carcinoma (IDC) of breast cancer, margin of error was 6% and confidence interval 95%.¹² All the females of age 18-65 years with histologically proven diagnosis of breast carcinoma were included in the study. The females with breast cancer and pregnant, were excluded.

The Ethical Review Committee approval was taken before conduction of the study and informed consents from all the eligible patients were obtained before collection of data. Socio-demographic data along with clinicopathological features and medical history were noted on predesigned proforma.

Immunohistochemistry (IHC) staining was performed for the evaluation of E-Cadherin expression and status of hormonal receptors [Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2-neu)]. The expression of HER-2 was confirmed by the technique of fluorescent in situ hybridization (FISH) in those patients which had equivocal result on immunohistochemistry (IHC). E-cadherin expression was examined semi-quantitatively by proportion of membrane-positive cells: 0 (0 to 10%); 1+ (10 to 30%); 2+ (30 to 70%); 3+ (>70%).^{13,14} The expression of E-cadherin was deemed positive, if the score was ≥ 2 ; and negative, if the score was ≤ 1 .

SPSS version 23 was used to analyse data. Mean and SD values were computed for numeric variables. Frequencies and percentages were computed for categorical and nominal variables. Chi-square test was applied to see the association between E-Cadherin expression and hormone status. Further, E-Cadherin expression was also stratified with respect to age and clinicopathological features, using Chi-square test. A p -value ≤ 0.05 was considered as statistically significant.

RESULTS

The mean age of the females with breast cancer was 47.88 ± 12.58 years. Majority of the females were married (82.3%), Unemployed (92.3%), had negative family history of breast cancer (88.3%); and almost half of the females had pre-menopausal status (52.4%). About 49.6% of the females had left breast cancer only 9.7% had bilateral disease. Majority of the patients had invasive ductal carcinoma (IDC, 80.2%), followed by invasive lobular carcinoma (ILC, 14.1%), not other-

wise specified (NOS, 4%), and only 1.6% had mixed type. More than half of the patients had tumour grade II (55.6%), 77.4% had tumour size greater than and equal to 2 cm, and 43.1% of them had lymph node status as N2 (Table I).

Table I: Descriptive statistics of study subjects (n=248).

Variables	Mean	SD
Age (years)	47.88	12.585
	n	%
Marital status		
Married	204	82.3
Unmarried	23	9.3
Widow	21	8.5
Employment status		
Unemployed	229	92.3
Employed	19	7.7
Menopausal status		
Pre-menopausal	130	52.4
Post-menopausal	118	47.6
Family history of breast cancer		
Negative	219	88.3
Positive	29	11.7
Laterality		
Right	101	40.7
Bilateral	24	9.7
Left	123	49.6
Histology		
IDC	199	80.2
ILC	35	14.1
NOS	10	4
Mixed	4	1.6
Grade		
I	15	6.0
II	138	55.6
III	95	38.3
Tumour size		
<2 cm	56	22.6
≥ 2 cm	192	77.4
Lymph node status		
No	18	7.3
N1	105	42.3
NII	107	43.1
NIII	18	7.3

The results of immunohistochemistry (IHC) showed that 82.7% of the tumours were E-cadherin positive, estrogen receptor (ER) positive status was found in 65.7%, progesterone receptor (PR) positive status was found in 62.9% and positive human epidermal growth factor receptor 2 (HER-2) expression was found in 29.4% of the patients (Figure 1).

There was a statistically significant relationship between E-Cadherin expression and age of the female ($p=0.003$). Majority of the females were in age group 35-60 years and the proportion of females was significantly higher in positive expression (66.8%) than negative expression (58.1%).

The relationship between menopausal status and E-Cadherin expression was statistically significant ($p=0.028$). Majority of the females, who had positive E-cadherin, were pre-menopausal (55.6%). About 67.8% of the patients had positive E-cadherin expression, who had negative HER-2 status; and statistically significant association was found between E-cadherin expression and HER-2 ($p=0.037$). The statistically significant

association was also found between E-cadherin and histological type of tumour, grade and size of tumour ($p < 0.05$, Table II).

Table II: Association of E-cadherin expression with hormonal receptors and other factors.

Variables	E-cadherin		p-value
	Negative (n=43)	Positive (n=205)	
Age groups			
<35 years	4(9.3%)	42(20.5%)	
35-60 years	25(58.1%)	137(66.8%)	
>60 years	14(32.6%)	26(12.7%)	
Menopausal status			
Pre-menopausal	16(37.2%)	114(55.6%)	0.028
Post-menopausal	27(62.8%)	91(44.4%)	
ER			
Negative	14(32.6%)	71(34.6%)	0.794
Positive	29(67.4%)	134(65.4%)	
PR			
Negative	17(39.5%)	75(36.6%)	0.716
Positive	26(60.5%)	130(63.4%)	
HER 2			
Negative	36(83.7%)	139(67.8%)	0.037
Positive	7(16.3%)	66(32.2%)	
Histological type			
IDC	21(48.8%)	178(86.8%)	<0.001
ILC	18(41.9%)	17(8.3%)	
NOS	0	10(4.9%)	
MIXED	4(9.3%)	0	
Tumour grade			
I	7(16.3%)	8(3.9%)	<0.001
II	30(69.7%)	108(52.7%)	
III	6(14%)	89(43.4%)	
Tumour size			
< 2cm	20 (46.5%)	36(17.6%)	<0.001
≥ 2 cm	23(53.5%)	169(82.4%)	
Lymph node status			
No	4(9.3%)	14(6.8%)	0.235
N1	19(44.2%)	86(42%)	
N2	20(46.5%)	87(42.4%)	
N3	0	18(8.8%)

Figure 1: Status of hormonal receptors.

DISCUSSION

The study results reflect the different socio-demographic features of patients of breast cancer. It showed that the mean age of the females with breast cancer was 47.88 ± 12.58 years; and almost half of the females had not reached to their menopause. However, in an Indian survey, the mean age of menopause women was found to be 46.2 years in Indian populace and 51 years in western population.¹⁵ The current study results also found that E-cadherin expression is positively associated with age of the females and menopausal status. The findings are in complete disagreement with the study suggesting no statistical significant association exists between E-cadherin expression and age of females or their menopausal status.^{16,17} The females, who were recruited in the present study, were 92.3% unemployed because of cultural factors, and majority of women stay at home as compared to the West.

The majority of the patients had invasive ductal carcinoma followed by invasive lobular carcinoma. Breast cancer's progression and capacity to invade and metastasise to distant sites is strongly associated with the loss of E-cadherin.¹⁸ It has been postulated that loss of E-cadherin expression is an early gate-keeper event in *in situ* lobular breast cancer and a precursor of invasive lobular breast cancer.^{19,20} Inactivating mutations in the CDH1 gene have been frequently described and can explain a great proportion of invasive lobular breast cancer cases. In a subsequent study, Berx and colleagues found somatic mutations of the E-cadherin gene at a comparable frequency, 56% (23 of 41) of lobular carcinoma cases, showing E-cadherin mutations.²¹ This high frequency of CDH1 mutations in breast cancer was not reported in all studies. Specifically, among the 23 mutations identified by Berx and colleagues,²¹ combination with LOH of the wild type CDH1 were found *locus*. These data were further validated by Huiping and colleagues,²² who detected LOH at 16q22.1 in all of the lobular breast tumours examined by their study. Currently, it is well established that 50% of invasive lobular carcinomas show LOH, which is determinant for protein dysfunction and loss of expression.

The current study results showed 82.7 of the tumours were E-cadherin positive, estrogen receptor (ER) positive status was found in 65.7%, progesterone receptor (PR) positive status was found in 62.9% and positive human epidermal growth factor receptor 2 (HER-2) expression was found in 29.4% of the patients. Horne *et al.* stratified estrogen receptor (ER) status and histological subtype among low E-cadherin patients and concluded that low expression of E-cadherin suggested low grade breast cancer and associated with tumour size of >2 cm having lobular histology and HER2-negative.²³

Singhai R *et al.* found a correlation between E-cadherin loss and invasive lobular carcinoma. However, he also found that no correlation existed among any prognostic variables of tumor. Diagnosis of invasive lobular carcinoma was made on the basis of negative E-cadherin stain having 88.1% sensitivity and 97.7% specificity. Moreover, E-cadherin expression was positive in patients diagnosed with tubulo-lobular carcinomas.²⁴

Yang Li *et al.* claimed that loss of E-cadherin was associated positively with metastasis of lymph node.¹² Fulgaet *et al.* concluded that E-cadherin is highly expressed in primary breast cancer sites as compared to metastatic sites.²⁵

The current study results also found that E-cadherin expression is associated with negative HER-2 status. The statistically significant association was also found between E-cadherin and histological type of tumour, grade and size of tumour ($p < 0.05$). The findings are in concordance with the study conducted by Parker *et al.*²⁶

The present study had its time constraints, therefore, more in-depth studies should be carried out. The expression of E-cadherin is yet to be studied in Asian population so that prognosis of breast carcinoma can be made easy. In a systemic review, odds ratio revealed strong association of E-cadherin expression with histopathological grading of tumours, tumour staging, tumour size, lymph node status, and hormone receptor status.⁵

CONCLUSION

There is a significant association between E-cadherin expression and hormone receptor status, HER2-neu, menopausal status, age of patients, grade of tumour and size of tumour. The present study had its time constraints, therefore, more in-depth studies should be carried out.

ETHICAL APPROVAL:

The Ethical Review Committee approval was taken before conduction of the study.

PATIENTS' CONSENT:

Informed consents from all the eligible patients were obtained before collection of data.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

AHA: Did the majority of manuscript writing, acquired all data by following up patients, and performed data analysis.

GH: Contributed to design of the work, final approval of the version to be published.

KA: Contributed to design of work data collection.

MH, PK, RI: Data collection and interpretation.

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