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Expression of E-Cadherin and P-Cadherin in Breast Carcinoma

Amira M. Bassam and Ahmed N. Eesa

Department of Pathology, Faculty of Medicine, Cairo University, Egypt

Abstract: This study aims to correlate immunohistochemical expression of P-cadherin and E-cadherin with pathological features of breast carcinoma in addition to correlation with estrogen and progesterone receptors status and expression of Her2-neu oncoprotein. The cross sectional study was conducted on 50 cases of female patients with breast cancer, admitted to Kasr Al-Ainy hospital. All cases were treated with modified radical mastectomy with complete dissection of axillary lymph nodes. Immunohistochemical staining for each case was conducted for both E-cadherin and P-cadherin. As regards expression of E-cadherin, 38 (76 %) cases were positive, while 12 (24 %) cases were negative. As regards expression of P-cadherin, 38 (76 %) cases were positive, while 12 (24 %) cases were negative. Among the study group, there was an association between expression of each of E-cadherin and P-cadherin and tumor histological type, where expression was significant among invasive ductal carcinomas (NOS), whether pure or mixed with other types. There was an association also between concomitant expression of E-cadherin, P-cadherin and of Her2-neu oncoprotein indicating aggressive tumor behavior. There was as well a strong concomitant expression of both cadherins (E & P). These findings need to be further substantiated with a prospective study supported by the use of molecular biological techniques to address the importance of P-cadherin expression as a prognostic factor for breast cancer patients and may support the development of new therapeutics to control carcinomas co-expressing both cadherins.

Key words: E-Cadherin · P-Cadherin · Breast Cancer

INTRODUCTION

The maintenance of adult tissue architecture largely depends on the structural and functional integrity of cadherins (CDs), a super family of Ca^{2+} dependent cell-cell adhesion molecules that usually mediate hemophilic and homotypic intercellular adhesion [1].

Classical E (Epithelial) and P (Placental) cadherins, which are preferentially located at the adherens type of intercellular junctions [2], share a common basic structure but have different molecular masses, binding specificities and tissue distribution [3].

Immunohistochemical studies have demonstrated that human E-CD is expressed in most epithelial tissues, whereas P-CD is restricted to the basal or lower layers of stratified epithelia, where it is frequently co-expressed with E-CD [4]. In breast tissue, E-CD is expressed in epithelial luminal cells, whereas P-CD is expressed in myoepithelial cells [5].

E-cadherin (Epithelial cadherin, CDH1) is a transmembrane glycoprotein responsible for cell-cell adhesion in epithelial tissues, being one of the most studied invasion suppressor proteins in cancer [6]. E-cadherin loss-of-function occurs during cancer progression [7] and is associated with tumors with an infiltrative pattern of growth, such as diffuse gastric and lobular breast cancers [8]. Somatic CDH1 mutations, as well as loss of heterozygosity, promoter hypermethylation or overexpression of transcriptional repressors, have been described as molecular mechanisms restraining E-cadherin normal function in invasive carcinomas [9].

Loss or delocalization of both catenins (p120ctn and βctn) from the membrane adhesion complex is usually related to an invasive cancer phenotype, due to cadherin destabilization and disorganization of the actin cytoskeleton [10]. However, some invasive epithelial tumors, namely the local advanced inflammatory breast cancer and some highly metastatic breast cancer cells,

Corresponding Author: Ahmed Naeem Eesa, Department of Pathology, Faculty of Medicine, Cairo University, Egypt.
Cell: 002-01110121353, E-mail: ahmed.naeem@kasralainy.edu.eg.

maintain normal membrane E-cadherin expression. Interestingly, these cells and tumors show aberrant concomitant expression of another epithelial cadherin, named P-cadherin (Placental cadherin, CDH3) [11].

P-cadherin is overexpressed in several solid tumors, including breast cancer, being expressed in 30% of all invasive carcinomas. It is associated with poor patient survival and is overexpressed in triple-negative basal-like carcinomas (TNBCs), which still do not have a targeted therapy [12]. One of the mechanisms underlying the invasive capacity of P- cadherin overexpression in breast cancer cells is mediated by the secretion of matrix metallo-proteinases (MMPs), which cleave its extracellular domain, producing a P-cadherin soluble fragment with pro-invasive activity [13].

The aim of this study is to estimate the correlation between both cadherins immunoreactivity and clinico-pathological data for female breast carcinomas, to evaluate their rule as prognostic markers and as possible therapeutic-targets.

MATERIALS AND METHODS

Study Design: The material of this retrospective cross-sectional study consists of 50 cases of female patients with breast cancer, admitted to Kasr Al-Ainy hospital where their paraffin blocks and copies of their pathology reports were available (From January 2012 to December 2012). All cases were treated with modified radical mastectomy with complete dissection of axillary lymph nodes.

Steps of the Work: Ages of all patients, tumor size and the presence or absence of metastatic axillary lymph nodes were recorded from the pathology report. The state of tumor stage was estimated according to TNM (2010 Revision based on *AJCC/UICC TNM, 7th edition*) [14].

The state of estrogen and progesterone immunoreactivity according to Allred/Quick score system was recorded from patient pathology reports, this system is based on the assessment of the proportion and intensity of staining: Score for proportion of cells with positive staining (0= no staining, 1=< 1% nuclear staining, 2=1-10% nuclear staining, 3= 11-33% nuclear staining, 4=34-66% nuclear staining, 5=67-100% nuclear staining) and score for intensity (0= no staining, 1= weak staining, 2= moderate staining, 3= strong staining). The scores are summed to give maximum of 8. Patients with scoring 2 or less are regarded as ER and PR negative and those with scoring above two are regarded as ER and PR positive [15].

The state of Her2/neu immunoreactivity was recorded according to a semiquantitative system based on the intensity of reaction product and percentage of membrane positive cells, giving a score range of 0 to 3+. No staining is observed, or membrane staining in fewer than 10% of tumor cells = score 0. A faint or barely perceptible membrane staining detected in more than 10% of tumor cells or the cells are only stained in part of the membrane = score 1+. A weak to moderate complete membrane staining is observed in more than 30% of tumor cells = score 2+. A strong complete membrane staining is observed in more than 30% of the tumor cells = score 3+. Samples scoring 3+ are regarded as unequivocally positive and those scoring 0/1+ as negative. Borderline scores of 2+ require confirmation with use of another analysis system, ideally FISH [15].

Three sections (5 microns thick) were prepared from each paraffin block, one of them was stained with hematoxylin & eosin for histopathological evaluation and the other two were mounted on poly-L-Lysine-coated slides (Super frost slides) and subjected to two immunohistochemical markers: E-cadherin and P-cadherin.

Hematoxylin & Eosin sections were evaluated for the type of breast carcinoma according to WHO classification [16] and histological grade according to Nottingham Grading System assigned by Elston and Ellis [17].

Immunohistochemical Staining for E-cadherin and P-cadherin: The sections were deparaffinized in xylene, then were hydrated through a series of graded alcohols (95%-70%), distilled water and phosphate buffered saline (At pH 7.5). The slides were then immersed in citrate buffer (pH 6) and were pretreated by microwave oven 800w for 20 minutes for antigen retrieval. After a 25 minute cooling period, the endogenous peroxidase activity was inhibited by incubation in 3% hydrogen peroxide (H_2O_2) for 5 minutes. After washing with Tris-buffered saline, the sections were incubated with the primary antibody for 1 hour at room temperature. The primary antibodies are rabbit polyclonal antibodies (61-0028-2 Genemed) and (NBP1-85707, Novus Biologicals), diluted at 1:100 in primary antibody diluent (Genemed).

The sections were washed in Tris-buffer and incubated with avidin-biotin-peroxidase system for 30 minutes. Peroxidase reaction was detected by addition of diamonobenzidine tetrahydrochloride. All slides were

rinsed well in tap water for 5 minutes then slightly counterstained with Hematoxylin for 1-2 minutes and dehydrated in ascending alcohol. The slides were cleared in xylene for 3 changes and then Canada balsam and cover slips were applied.

Evaluation of E-cadherin and P-cadherin Expression: The immunoreactivity with E-cadherin was scored as follows: A strong inter-membranous staining in most of the tumor cells was scored as 3+ and a moderate staining in >10 % of the cells was scored as 2+, while a weak staining in < 10 % cells was scored as 1+ and an absence of membrane staining was scored as 0 [18]. Samples scoring 3+ and 2+ are regarded as positive and those scoring 0/1+ as negative. The immunoreactivity with P-cadherin (Cytoplasmic and membranous) was scored as follows: no staining or < 20% of cells staining was scored as 0 and 20-50% of cells staining was scored as 1+, while 51-80% of cells staining was scored as 2+ and > 80% of cells staining was scored as 3+ [19]. Samples scoring 3+ and 2+ are regarded as positive and those scoring 0/1+ as negative.

Statistical Analysis: Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21. Comparisons between the two groups with respect to normally distributed numeric variables were done using the t-test. Non-normally distributed numeric variables were compared by Mann-Whitney test. For categorical variables, differences were analyzed with χ^2 (Chi square) test and Fisher's exact test when appropriate. All p-values are two-sided. P-values < 0.05 were considered significant.

RESULTS

This retrospective study was conducted on fifty cases of breast carcinoma in females. Their ages ranged from 28 to 70 years with mean age 49 years. As regards the histological type of breast cancer, 34 (68%) cases were classified as invasive duct carcinoma, 6 (12%) cases were classified as invasive lobular carcinoma and 10 (20%) of cases as mixed invasive duct and lobular carcinoma. All cases of invasive duct carcinoma were NOS (Fig. 1) except one case showed invasive papillary features (Fig. 2). As regards the histological grade, 41 (82%) of cases were grade II and 9 (18%) cases were grade III. As regards the tumor stage (T stage), 6 (12%) cases presented with T1, 27 (54%) cases presented with T2, 10 (20%) cases presented with T3 and 7 (14%) cases

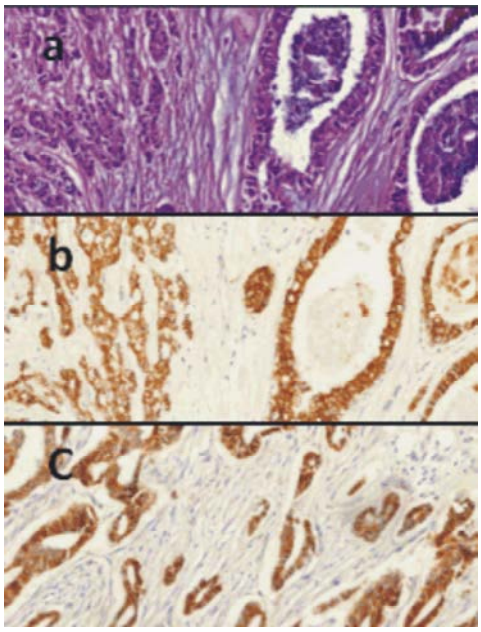

Fig 1: Invasive Duct Carcinoma, Grade II, a). H&E. b). E-cadherin positive c). P-cadherin positive (100x).

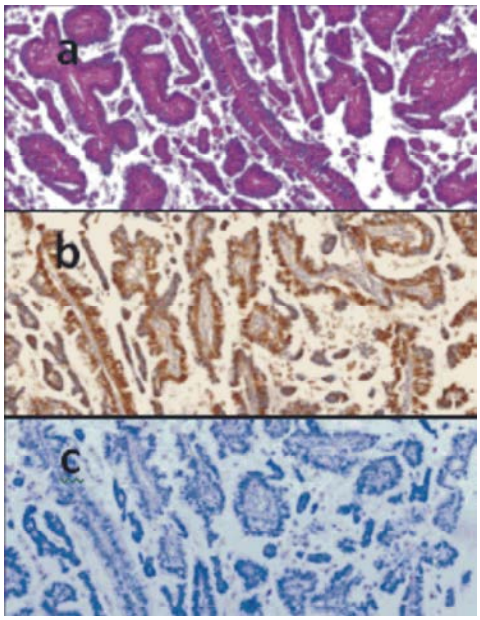

Fig 2: Invasive Papillary duct Carcinoma, a). H&E. b). E-cadherin positive. c). P-cadherin negative. (100x)

presented with T4. As regards the tumor size, it ranged between 1.5 and 12 cm with a median of 3.5 cm. As regards lymph node status,12 (24%) cases had no lymph node metastatic deposits N0 and 38 (76%) cases presented lymph node metastasis. 9 (18%) cases presented with N1, 13 (26%) presented with N2 while 16 (32%) cases presented with N3. As regards estrogen receptors status,

34 (68%) cases were positive for estrogen receptors while 16 (32%) cases were negative. As regards the progesterone receptors status, 28 (56%) cases were positive for progesterone receptors while 22 (44%) cases were negative. As regards the Her2/neu oncoprotein status, 10 (20%) cases were positive for Her2/neu oncoprotein while 40 (80%) cases were negative. As regards expression of E-cadherin, 38 (76 %) cases were positive for E-cadherin (expressed), while 12 (24 %) cases were negative (not expressed). As regards expression of P-cadherin, 38 (76 %) cases were positive for P-cadherin (Expressed), while 12 (24 %) cases were negative (Not expressed). Correlation between the clinico-pathological variables and expression of E-cadherin among the study group showed a non-statistically significant correlation except for tumor histological type and Her2/neu expression (Table 1). Expression was notably significant among invasive ductal carcinoma both pure and mixed types. All cases of pure invasive lobular carcinoma were negative for E- cadherin. In our study, all cases expressing Her2/neu oncoprotein also expressed E-cadherin. Correlation between the expression of P-cadherin and expression of E-cadherin among the study group showed a statistically significant correlation (Table 1). This is to say, there is a strong concomitant expression of both markers. Also, correlation between the clinico-pathological variables and expression of P-cadherin among the study group showed a non-statistically significant correlation except for tumor histological type and Her2/neu expression (Table 2). Expression was notably significant among invasive ductal carcinoma both pure and mixed types. 5 out of 6 cases of pure invasive lobular carcinoma were negative for P- cadherin. In our study, all cases expressing Her2/neu oncoprotein also expressed P- cadherin.

DISCUSSION

The present study demonstrated that membranous expression of E-cadherin was significantly associated with tumor histological type and expression of Her2/neu oncoprotein. Expression was notably significant among

Table 1: Relationship between E-cadherin expression and clinico-pathological variables

	E-cadherin expression				
Factors	Negative n=12(%)	Positive n=38(%)	Test value	P value	Significance
Age (yrs.)					
Mean ±SD	51.5±10.7	52.3±10.7	t=-0.236	0.814	NS
Tumor Size(cm)					
Median (range)	2.6(1.5-12.0)	3.5(1.5-12.0)	z=-1.678	0.093	NS
Histological type					
Duct Carcinoma	5(41.7)	29(76.3)	Fisher=17.38	<0.001	Significant
Lobular carcinoma	6(50.0)	0			
Mixed type	1(8.3)	9(23.7)			
Grade					
II	9(75.0)	32(84.2)	x^2=0.524	0.469	NS
III	3(25.0)	6(15.8)			
Lymph nodes					
-Ve	3(25.0)	9(23.7)	x^2=0.009	0.926	NS
+Ve	9(75.0)	29(76.3)			
Estrogen receptors					
-Ve	5(41.7)	11(28.9)	x^2=0.678	0.410	NS
+Ve	7(58.3)	27(71.1)			
Progesterone receptors					
-Ve	5(41.7)	17(44.7)	x^2=0.035	0.852	NS
+Ve	7(58.3)	21(55.3)			
Her2/neu					
-Ve	12(100.0)	28(73.7)	x^2=3.943	0.047	Significant
+Ve	0	10(26.3)			
P-cadherin					
-Ve	6(50.0)	6(15.8)	x^2=5.852	0.016	Significant
+Ve	6(50.0)	32(84.2)			

Table 2: Relationship between P-cadherin expression and clinico-pathological variables

Factors	P-cadherin expression Negative n=12(%)	 Positive n=38(%)	Test value	P value	Significance
Age (yrs.)					
Mean ±SD	54.1±11.6	51.5±10.4	t=0.721	0.475	NS
Tumor Size(cm)					
Median (range)	3.5(1.5-9.0)	3.4(1.6-12.0)	z=-0.468	0.640	NS
Histological type					
Duct carcinoma	4(33.3)	30(79)	Fisher=12.42	0.001	Significant
Lobular carcinoma	5(41.7)	1(2.6)			
Mixed type	3(25.0)	7(18.4)			
Grade					
II	10(83.3)	31(81.6)	x^2=0.019	0.890	NS
III	2(16.7)	7(18.4)			
Lymph nodes					
-Ve	4(33.3)	8(21.1)	x^2=0.754	0.448	NS
+Ve	8(66.7)	30(78.9)			
Estrogen receptors					
-Ve	2(16.7)	14(36.8)	x^2=1.706	0.192	NS
+Ve	10(83.3)	24(63.2)			
Progesterone receptors					
-Ve	4(33.3)	18(47.4)	x^2=0.729	0.393	NS
+Ve	8(66.7)	20(52.6)			
Her2/neu					
-Ve	12(100.0)	28(73.7)	x^2=3.943	0.047	Significant
+Ve	0	10(26.3)			

invasive ductal carcinoma both pure and mixed types. All cases of pure invasive lobular carcinoma were negative for E- cadherin. In our study, all cases expressing Her2/neu oncoprotein also expressed E-cadherin. However, no significant correlations were regarded with tumor grade, tumor size, stage or lymph node metastasis.

Fanelli *et al*. [20] and colleagues stated that E-cadherin immunostaining was absent in invasive lobular carcinoma (ILC). In a study by Kanthilatha *et al.* [18] results support our work, they found a highly significant correlation of the E-cadherin expression with the histological phenotype of the tumors. 26 of the 28 cases of IDC showed a moderate to strong membrane (2+/3+) expression of E-cadherin, while only 1/28 cases of ILC showed a 2+ staining. Similar findings were also reported by Singhai *et al.* [21] in a large series of cases of breast cancer that showed a significant statistical correlation of the E-cadherin loss with a positive diagnosis of invasive lobular carcinoma and a negative E-cadherin stain confirmed the diagnosis of invasive lobular carcinoma with 97.7% specificity; 96.8% negative predictive value; 88.1% sensitivity; and 91.2% positive predictive value.

Concerning Her 2/neu expression, our results agreed with Ribeiro *et al.* [22] who reported an association between expression of E-cadherin and overexpression of Her2/neu, suggesting that E-cadherin expression might be an ominous prognostic indicator. Hofmann *et al.* [23] found that there is no correlation was seen between serum E-cadherin levels and hormone receptor and menopausal status as well as Her2/neu status.

As regards tumor grade, size, stage or lymph node metastasis, previous studies on human breast cancer have reached similar observations [19] or have associated preservation of expression of E-cadherin with lymph node metastasis [24].

One previous report on canine mammary tumors showed no association between reduced E-cadherin expression and high histological grade [25]. In human cancer studies, they also found similar results for tumor differentiation [19, 24]. However, other studies on canine mammary tumors had found a relationship [26, 27]. These results suggest a possible role for E-cadherin-mediated adhesion in preventing invasion and metastasis in canine mammary tumors, supporting some studies in human breast cancer [28, 29].

Results of present study as regards correlation between expression of E-cadherin and hormone receptors status (ER and PR) support a previous study by Kowalski and colleagues [30], who did not find an association between E-cadherin expression and the ER and PR. Other studies had observed a correlation between reduced E-cadherin expression and ER and PR status [31].

Sample selection (Histological type, stage, tumor grade), number of cases analyzed and differences in staining evaluation, genetic and geographic variations may individually or in combination be held responsible for the observed discrepancies between different studies.

In the present study, we described an association between expression of P-cadherin and tumor histological type and expression of Her2/neu oncoprotein but we did not find further associations between P-cadherin expression and other clinicopathological variables. This means that expression of P-cadherin was notably significant among invasive ductal carcinoma both pure and mixed types. 5 out of 6 cases of pure invasive lobular carcinoma were negative for P- cadherin. In our study, all cases expressing Her2/neu oncoprotein also expressed P- cadherin.

Results of our study was similar to that by Fanelli *et al.* [20] they stated that P-cadherin immunostaining was absent in ILC. This association with tumor histological type was also found by Gama *et al.* [32] in canine mammary tumors and was not confirmed in a later study performed by the same team in 2008 [33]. In human cancer studies we also find contradictory results, probably related with sample selection. Paredes *et al*. [34] and coworkers found no significant correlation with histological type and some authors suggested that P-cadherin was related with some special tumor types, such as medullary and metaplastic carcinomas [35].

The present work supports a previous study by Gama *et al.* [32] which did not find a statistically significant difference between P-cadherin aberrant expression and differentiation grade. However contradictory results were observed by Fanelli *et al*. [20] and coworkers who had observed a significant association between P-cadherin negative cases and low tumor grade (p=0.0056). Moreover, in recent studies on human breast cancer, P-cadherin expression was significantly associated with increased histological grade [19, 34, 35]. These studies thus suggested P-cadherin expression as a marker of bad prognosis and might play role in tumor progression. Interestingly, none of these reports showed a significant association with tumor size.

Indeed, in several studies addressing invasive breast carcinomas, P-cadherin expression is normally directly associated to Her2/neu expression, which is in accordance with the results obtained in our study [22, 36].

Many studies have reported that P-cadherin expression in breast carcinomas is inversely related with hormonal receptors content; the majority of the cases are ER and PR negative [20, 34].

Some studies on human breast cancer [19, 34, 35] also failed to find a correlation between anomalous expression of P-cadherin and the presence of lymph node metastases. However, other studies have described an association with highly proliferative tumors [34], lymph node metastases [20] and poor prognosis [34, 35].

Although several authors suggested a possible role for P-cadherin in promoting aggressive tumor cell behaviour [34, 37], the biological significance of the anomalous P-cadherin in breast cancer is still poorly understood. As P-cadherin is expressed only by myoepithelial cells in normal breast tissue, the presence of this molecule might indicate a basal/myoepithelial differentiation [37], which has been associated with a poor outcome in human breast cancer [38].

Our study stated that there is a strong concomitant expression of both markers (E-cadherin and P-cadherin). Paredes *et al.* [11] and Paredes *et al.* [36], stated that that P-cadherin expression has a relevant role in the prognosis of invasive breast cancer that maintains E-cadherin expression, thus can be classified as a biomarker of poor prognosis in E-cadherin positive breast carcinomas. A study by Ribeiro *et al*. [22] showed that P-cadherin overexpression in an E-cadherin wild-type context is an alternative mechanism for cancer invasion, disrupting the interaction between E-cadherin and intracellular catenins and leading to alterations in biological behaviour and the gene expression profile of breast cancer cells. They reinforce the importance of P-cadherin expression as a prognostic factor for breast cancer patients and support the development of new therapeutics to control aggressive carcinomas co-expressing both cadherins.

CONCLUSION

There is an association between expression of both E-cadherin and P-cadherin and tumor histological type in breast carcinoma. Expression was notably significant among invasive ductal carcinoma both pure and mixed types. There is an association between expression of both E-cadherin and P-cadherin and expression of Her2/neu oncoprotein in breast carcinoma. All cases expressing Her2/neu oncoprotein also expressed E- cadherin and

P-cadherin which may impart unfavorable prognosis. There is a strong concomitant expression of both cadherins (E-cadherin & P-cadherin) in breast carcinoma that may suggest a role in tumor progression. These findings need to be further substantiated with a prospective study supported by the use of molecular biological techniques to address the importance of P-cadherin expression as a prognostic factor for breast cancer patients.

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