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ORIGINAL ARTICLE

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P-cadherin expression is associated with high-grade ductal carcinoma in situ of the breast

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Abstract Cadherins are calcium-dependent cell–cell adhesion glycoproteins, separated into several subclasses with distinct adhesive specificities and tissue distribution, which play an important role in many cellular events. We analyse the expression of E-, N- and P-cadherin in a series of ductal carcinoma in situ (DCIS) of the breast, since this disease represents a heterogeneous group, with different risks of progression to invasive breast carcinoma. We also studied the correlation between cadherin expression and DCIS classification systems, namely the Van Nuys and the Holland et al. classification, this latter based on cytonuclear differentiation and cell polarity. Our results showed that, regardless the classification applied, P-cadherin expression is strongly associated with high histological grade of DCIS (P=0.0047) and lack of estrogen receptors (P=0.0008). The use of Holland et al. classification showed a significant correlation between P-cadherin expression and decreased cell polarity (P=0.01). In conclusion, P-cadherin expression seems to be more relevant in DCIS pathogenesis than the altered expression of any other cadherin, including the decrease of E-cadherin expression.

Keywords Cadherins · Ductal carcinoma in situ of the breast · P-cadherin · E-cadherin · Cell polarity

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Introduction

Cadherins are a family of glycoproteins expressed on the cell surface, which act as intercellular adhesion molecules by calcium-dependent homophilic binding [9, 38]. Their structural and functional integrity play a role in cell sorting during embryogenesis and in the maintenance of adult tissue architecture [9, 38]. Intracellularly, these transmembrane molecules form complexes with several proteins [41] and cytoskeleton components that constitute the intercellular adherens junctions and mediate signal-transduction mechanisms to control cellular events, including cell polarity, differentiation, growth and migration [18, 42].

The classical cadherins, namely epithelial (E-), neural (N-) and placental (P-) cadherin, originally described by their tissue specificity, have been used as markers in the identification of benign tissues and some neoplastic processes [11, 12, 13, 26, 37, 38, 41]. Nowadays, the study of cadherins has been focused on their possible role in carcinogenic pathways. In normal adult breast, E-cadherin is expressed in both luminal epithelial cells and myoepithelial cells, whereas P-cadherin is present only in myoepithelial cells [25, 28, 32]. The expression of N-cadherin is not found in normal breast tissue [11, 17, 29, 36].

The role of E-cadherin in breast cancer has been explored in the last few years and its lack or decreased expression has been correlated with tumour grade, invasiveness and prognosis [4, 5, 7, 34, 39], especially in lobular carcinomas, which have a high frequency of mutations in the E-cadherin gene [2, 3, 22].

N- and P-cadherin expression in breast carcinoma is still poorly understood. Recent studies have shown that N-cadherin in breast cancer cell lines contributes to a diffuse phenotype and promotes motility, invasion and metastasis [14, 24]. P-cadherin, however, can be expressed in a subset of breast cancers [25, 28]. Recently, Peralta Soler et al. observed P-cadherin expression in invasive ductal carcinomas with higher histological grade and poor survival, suggesting that this protein could constitute a prognostic marker [27].

Ductal carcinoma in situ (DCIS) represents a heterogeneous group of lesions which is manifested in clinical and radiological presentation, histological appearance, expression of biological markers and, most significantly, in biological behaviour, with different risks of progression to invasive breast carcinoma [19, 33]. The several classification systems in use reflect the heterogeneity of these lesions. Van Nuys classification, a combination of nuclear grade and necrosis evaluation, seems to predict clinical recurrence [35]. Holland et al. proposed a different system of classification based on cytonuclear morphology and architectural differentiation (cellular polarisation) [15], and this latter criterion could be correlated with cadherins expression, since one of the major functions of them is to maintain the epithelial cell polarity.

We analysed the expression of E-, N- and P-cadherin in a series of DCISs of the breast and its correlation with other biological markers in attempt to study the possible role of cadherins in the different histotypes of DCIS.

Materials and methods

Tumour specimens

Formalin-fixed, paraffin-embedded blocks of 73 ductal carcinomas in situ of the breast were retrieved from the histopathology files of our institutes. All cases were reviewed on haematoxylin and eosin stained sections by three pathologists (F.S., F.M., L.V.). Histological typing and grading were performed in accordance with two types of DCIS classification: the Van Nuys classification, presented by Silverstein et al. [35], and the classification proposed by Holland et al. [15]. The Van Nuys classification, which consists of a combination of tumour nuclear grade and extent of necrosis, defines three distinct recognisable groups: (i) non-high grade DCIS without comedo-type necrosis, (ii) non-high grade DCIS with comedo-type necrosis and (iii) high grade DCIS with or without comedo-type necrosis [35]. Holland's proposal, based on nuclear morphology and cell polarisation (architecture), divides DCIS cases into well differentiated (type I) and poorly differentiated (type III) tumours. Cases with an intermediate differentiation are included in type-II DCIS [15].

All relevant data were available for analysis, including age, tumour size, estrogen receptor status, and p53, c-erbB-2 and cyclin D1 expression. The mean age of the patients at diagnosis was 55 years (range 32–78 years). The size of the tumours ranged from 4.5 mm to 125.0 mm (mean 31.8 mm±28.9 mm).

Immunohistochemistry

Three-micron-thick sections were immunostained with monoclonal antibodies against E-cadherin (HECD-1, 1:200, Zymed Laboratory, San Francisco, Calif.), P-cadherin (clone 56, 1:50, Transduction Laboratories, Lexington, Ky.) and N-cadherin (clone 3B9, 1:400, Zymed Laboratory). Immunostainings were performed using the avidin–biotin–peroxidase (ABC) complex. Antigen retrieval was carried out by microwave treatment in a 0.05% detergent solution for E- and N-cadherin antibodies, and with 10 mM citrate buffer, pH 6.0 (Dako Corporation, Carpinteria, Calif.) for P-cadherin antibody. After cooling at room temperature, the sections were immersed in 3% hydrogen peroxide (H_2O_2) and methanol to block endogenous peroxidase activity. Non-specific staining was eliminated by incubation with normal rabbit serum (Dako), and the specific monoclonal antibodies were incubated overnight at 4°C in a humid chamber. After washing the slides, sections were incubated with a 1:200 dilution of biotin-labelled secondary antibody followed by ABC complex (avidin, 1:100 and biotin-labelled peroxidase, 1:100). These reagents were purchased from Dako. Subsequently, sections were stained with a solution of 3,3-diaminobenzidine tetrahydrochloride (DAB) with H_2O_2 in Tris-HCl buffer, pH 7.6 (LabVision Corporation, Fremont, Calif.), counterstained with Mayer's haematoxylin, dehydrated, and mounted.

Positive and negative controls were included in all series for all the antibodies used. Paraffin sections of normal skin tissue were used as positive control for E-cadherin, normal breast tissue for P-cadherin and cardiac muscle for N-cadherin. Immunohistochemical results were not assessed in ten cases (six for E-cadherin and four for P-cadherin), since there was no more tumour material available.

Quantification of immunostaining

The DCIS presenting cells with an unequivocal membranous staining for the three cadherins tested were scored as positive. Cells with cytoplasmic expression alone were not considered. The assessment of immunohistochemical results was based on a semiquantitative evaluation proposed by Han et al. [12], which does not include the intensity of staining. The cases were separated into four groups according to the percentage of immunopositive cells: 0, <10%; 1, 10–25%; 2, 26–50%; 3, >50%. The expression of cadherin was considered positive if staining was identified in at least 10% of the cells in the expected cell–cell membrane location.

Statistical analysis

For statistical analysis, contingency tables and chi-square test were done using StatView 5.0 (SAS Institute Inc., Cary, N.C.) to estimate the relationship between staining patterns of the different antibodies used. Two values were considered significantly different when $P<0.05$.

Results

Of the 73 cases that were reviewed and graduated by Van Nuys classification, 10 (13.7%) were classified as grade-I, 18 (24.7%) as grade-II and 45 (61.6%) as grade-III tumours. Using Holland et al. classification, 10 cases were considered well-differentiated tumours (13.7%), 13 were intermediately differentiated (17.8%) and 50 cases were included in the poorly differentiated group (68.5%).

P-cadherin was positive in 23 (33.3%) cases and negative in 46 (66.7%) cases of DCIS. Distribution of P-cadherin in tumour cells showed membranous staining frequently associated with cytoplasmic expression (Fig. 1). Myoepithelial cells were always positive for P-cadherin in normal ducts and in ducts containing in situ carcinoma.

Regardless of the classification applied, P-cadherin expression showed a strong correlation with high histological grade, since this protein was essentially present in grade-III (poorly differentiated) tumours, while grade-I (well differentiated) cases were all negative for P-cadherin (Table 1 and Table 2). We correlated separately the expression of each cadherin with the two parameters used in Holland's system: cytonuclear and architectural differentiation (cellular polarisation). Our results showed that expression of P-cadherin is related to loss of cell polarity (P=0.01), as well as with nuclei pleomorphism (P=0.0072; Table 3 and Table 4).

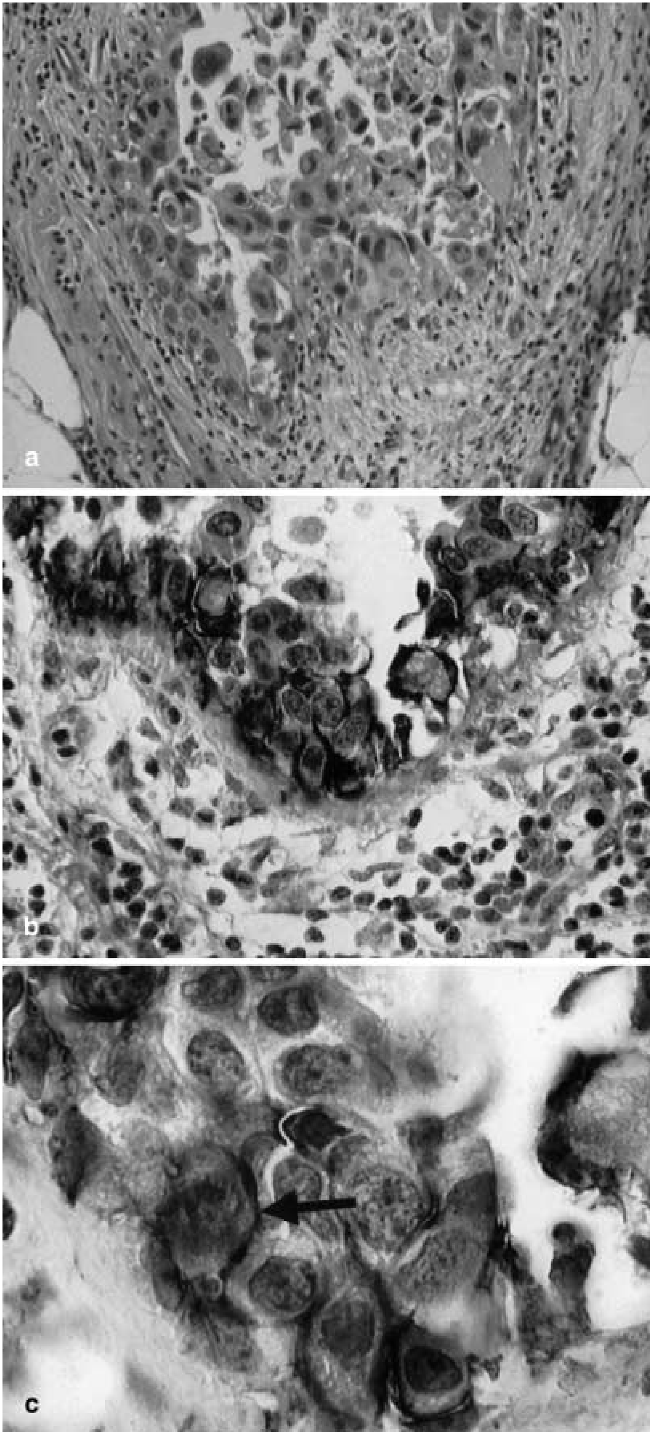

Fig. 1 **a** Ductal carcinoma in situ (DCIS) of the breast with high histological grade (poorly differentiated). Haematoxylin and eosin ×200. **b** Strong expression of P-cadherin in a poorly differentiated DCIS of the breast; ×400. **c** Higher magnification of P-cadherin membranous staining; ×1000 (*black arrow*)

Statistical analysis of the data revealed an inverse correlation between P-cadherin expression and estrogen receptor status: 60.9% of P-cadherin positive cases were estrogen receptor negative (Table 5). The chi-square test showed that this difference was statistically significant (P=0.0008).

The comparison between cases with positive and negative P-cadherin expression was performed for p53, c-erbB-2 and cyclin D1: 86.9% of the cases c-erbB-2 positive have demonstrated P-cadherin positivity (P=0.015); the expression of p53 was also higher in P-cadherin positive cases than in negative cases (P=0.0544), but no significant correlation was found with cyclin D1. Some difference in tumour size was found between cases with P-cadherin positive (41.9 mm±34.2 mm) and P-cadherin negative (28.3mm±26.0 mm) tumours, although it was not statistically significant (P=0.0871).

Most of the cases were positive for E-cadherin (89.4%), showing a clear and strong membranous staining of the neoplastic epithelial cells, particularly along their lateral and basal membranes (Fig. 2). In contrast to P-cadherin, expression of E-cadherin was lower in high-grade DCIS: 71.4% of E-cadherin negative cases were grade-III tumours.

N-cadherin was only found in 12.3% of the tumours, and its expression was restricted to a small population of cells, which presented a faint membranous staining, always associated with a strong expression in the cytoplasm. There was no correlation between N-cadherin expression and histological grade or any other parameter studied.

Discussion

The present study shows that P-cadherin expression is strongly associated with high histological grade of DCIS and with loss of ER, as already reported by two other studies in invasive ductal carcinoma [25, 27]. Moreover, almost all P-cadherin-positive cases were also positive to c-erbB-2, and some have presented p53 immunoreactivity. All these biological conditions were already reported as correlated with poor differentiation in DCIS [19, 33].

Our results also demonstrated a relationship between P-cadherin expression and loss of tumour cell polarity, one of the parameters of the DCIS classification proposed by Holland et al. [15]. Cell polarity is an indicator and a determinant of cellular differentiation, and adhesion molecules provide the spatial structure to the establishment of a polarised epithelium [6, 21]. The progression of the normal polarised epithelial phenotype to the malignant invasive phenotype could be attributed in part to a loss of intercellular adhesion mediated by E-cadherin, with a resulting increase in cell motility and loss of cell polarity. Recent studies have suggested that, in breast epithelia, other mechanisms should be able to establish apical/basal domains at the morphological level [8, 39], which probably are downregulated in some cases of DCIS, inducing loss of cell polarity without loss of E-cadherin expression. P-cadherin could be one of the proteins responsible for loss of cell polarity, since it mediates weaker and unstable cell–cell contacts that are easily broken and reformed [43], which could not maintain the differentiated epithelia. In this context, P-cadherin

Table 1 Correlation between P-, E- and N-cadherin expression and Van Nuys classification [31]

	P-cadherin		E-cadherin		N-cadherin	
	Positive	Negative	Positive	Negative	Positive	Negative
Total	23	46	59	7	9	64
GI	0 (0%)	10 (21.8%)	9 (15.3%)	1 (14.3%)	2 (22.2%)	9 (14.1%)
GII	3 (13.0%)	14 (30.4%)	16 (27.1%)	1 (14.3%)	1 (11.1%)	16 (25.0%)
GIII	20 (87.0%)	22 (47.8%)	34 (57.6%)	5 (71.4%)	6 (66.7%)	39 (60.9%)
P value	0.0047	0.7387	0.5933			

Table 2 Correlation between P-, E- and N-cadherin expression and the classification proposed by Holland et al. [15]. *Wd* well-differentiated tumours, *Id* intermediately differentiated tumours, *Pd* poorly differentiated tumours

	P-cadherin		E-cadherin		N-cadherin	
	Positive	Negative	Positive	Negative	Positive	Negative
Total	23	46	59	7	9	64
Wd	0 (0%)	9 (19.6%)	8 (13.6%)	1 (14.3%)	2 (22.2%)	8 (12.5%)
Id	2 (8.7%)	11 (23.9%)	12 (20.3%)	1 (14.3%)	1 (11.1%)	12 (18.8%)
Pd	21 (91.3%)	26 (56.5%)	39 (66.1%)	5 (71.4%)	6 (66.7%)	44 (68.7%)
P value	0.0105	0.9298	0.6676			

Table 3 Correlation between P-, E- and N-cadherin expression and cytonuclear pleomorphism (size, outline, chromatin, nucleoli, mitoses)

	P-cadherin		E-cadherin		N-cadherin	
	Positive	Negative	Positive	Negative	Positive	Negative
Total	23	46	59	7	9	64
Monomorphic	1 (4.3%)	8 (17.4%)	9 (15.3%)	1 (14.3%)	2 (22.2%)	8 (12.5%)
Pleomorphic	2 (8.7%)	16 (34.8%)	16 (27.1%)	1 (14.3%)	1 (11.1%)	17 (26.6%)
Marked pleomorphic	20 (86.9%)	22 (47.8%)	34 (57.6%)	5 (71.4%)	6 (66.7%)	39 (60.9%)
P value	0.0072	0.7387	0.509			

Table 4 Correlation between P-, E- and N-cadherin expression and the architectural differentiation (cell polarisation)

	P-cadherin		E-cadherin		N-cadherin	
	Positive	Negative	Positive	Negative	Positive	Negative
Total	23	46	59	7	9	64
Absent	18 (78.3%)	21 (45.6%)	35 (59.3%)	2 (28.6%)	4 (44.4%)	38 (59.4%)
Present	5 (21.7%)	25 (54.4%)	24 (40.7%)	5 (71.4%)	5 (55.6%)	26 (40.6%)
P value	0.01	0.1212	0.3962			

Table 5 Correlation between P-cadherin expression and size of the tumour, estrogen receptor status, and c-erbB-2, p53 and cyclin D1 positive expression

	P-cad+	P-cad–	*P* value	E-cad+	E-cad–	*P* value	N-cad+	N-cad–	*P* value
Size (mm)	41.9±34.2 (20)	28.3±26.0 (43)	0.0871	35.1±30.2 (55)	13.2±9.4 (6)	0.086	17.5±13.8 (8)	31.7±29.5 (54)	0.1869
ER	39.1% (9/23)	80.0% (36/45)	0.0008	67.2% (39/58)	85.7% (6/7)	0.3172	66.7% (6/9)	68.3% (43/63)	0.9239
c-erb-B2	86.9% (20/23)	57.7% (26/45)	0.015	67.8% (40/59)	50.0% (3/6)	0.3801	77.8% (7/9)	65.1% (41/63)	0.4497
P53	39.1% (9/23)	17.7% (8/45)	0.0544	20.3% (12/59)	28.6% (2/7)	0.6144	44.4% (4/9)	22.2% (14/63)	0.1498
Cyclin D1	82.6% (19/23)	80.4% (37/46)	0.8277	76.3% (45/59)	100% (7/7)	0.1465	88.9% (8/9)	78.1% (50/64)	0.4543
Total	23	46		59	7		9	64	

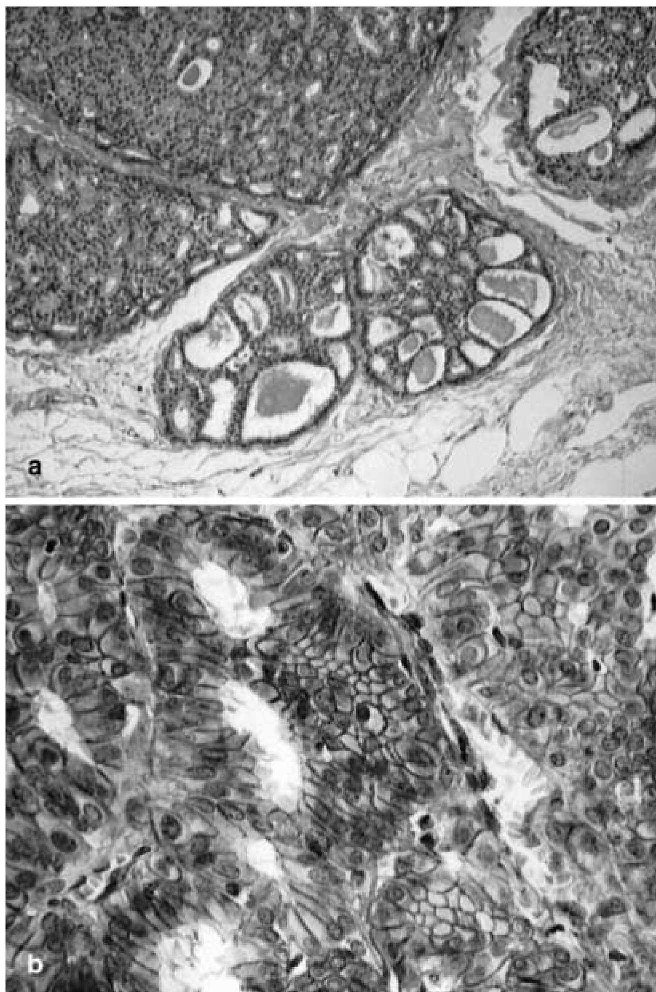

Fig. 2 **a** Ductal carcinoma in situ (DCIS) of the breast with low histological grade (well differentiated). Haematoxylin and eosin ×200. **b** Cell-membrane pattern of E-cadherin expression in a well-differentiated DCIS of the breast; ×400

aberrant expression in E-cadherin positive cells could interfere with the normal adhesion system.

In addition, the results provide evidence that P-cadherin is probably involved in early steps of breast carcinogenesis, activating mechanisms responsible for cell proliferation, which is higher in cells of poorly differentiated DCIS [23]. In fact, P-cadherin constitutes a molecule that is always present in normal cells with high proliferation rate, like the basal layers of stratified epithelia.

The expression of P-cadherin by breast cancer cells has been explained by several hypotheses. Palacios et al. suggested that its expression in breast carcinomas could indicate a proliferative ability acquired by tumour cells with high mitotic index, to respond to E-cadherin downregulation and to maintain cancer cells nests [25]. An alternative is that P-cadherin could be a member of an oncofetal protein family, since it is highly present in embryogenesis stages and weakly and focally expressed in the adult tissues [25]. More recently, Soler et al. advanced that the expression of P-cadherin by tumour cells could be related to a histogenetic origin in cap cells or in the acquisition of a phenotype with characteristics similar to this type of cell [27]. Cap cells constitute a single layer of growing cells located at the tip of the end buds during the development of mammary glands and represent a stem cell population in the adult breast, specialised in paving the way for ductal elongation as well as serving as precursors to myoepithelial cells [30]. The higher proliferation rate of cap cells, the absence of ER expression and the ability to differentiate into myoepithelial cells suggest that they could be responsible for development of some types of breast cancer cells [27, 30, 31].

The association between E-cadherin expression and DCIS histological grade was not statistically significant. In contrast with lobular carcinoma in situ (LCIS), where E-cadherin alterations [mutations and loss of heterozygosity (LOH)] are frequently present indicating that this is an early event in lobular neoplasia [40], only 7 of our 73 cases of DCIS were negative for E-cadherin. Some authors have recorded a correlation between reduced expression of E-cadherin and the grade of malignancy of DCIS [10], but most of them have failed to find any relationship [1, 22]. Recent studies have demonstrated that E-cadherin immunostaining could be a valuable tool in the distinction between DCIS and LCIS, since the former are usually E-cadherin positive [16, 20]. With regard to N-cadherin expression in breast DCIS, it failed to correlate with histological grade or any other factor, as reported recently in invasive cases [27].

The distinct patterns of P-, E- and N-cadherin expression observed in this study suggest a differential role for these cadherins in DCIS. We conclude that P-cadherin expression in DCIS is associated with a high histological grade, probably due to loss of cell polarisation and increase of proliferation, and it seems to be more relevant in DCIS pathogenesis than the altered expression of any other cadherin, including the decrease of E-cadherin expression.

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