

E-cadherin expression in molecular types of breast carcinoma

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Abstract

E-cadherins are epithelial morphological stabilizers, performing complex functions as receptors, providers of cellular and tissular structural integrity, and functional interactive mediators. Structural and functional unbalance initiated due to E-cadherin expression loss results in direct effects on carcinogenesis specific biological processes, as cellular invasion and proliferation. We investigated the E-cadherin expression aiming (i) to identify the differences in the molecular subtypes of breast cancer, (ii) to analyze the correlations between E-cadherin and specific clinicopathological and molecular characteristics. The study included 42 cases that were investigated immunohistochemically using a panel of antibodies (ER, PR, Her2/neu, CK5/6, EGFR), which permitted a diagnostic in compliance with the molecular classification, followed by the E-cadherin evaluation. The semi-quantitative assessment of E-cadherin was performed using a scoring system based on the positive cells percentage and the staining intensity. Our results showed, according to the molecular subtypes, a strong positive E-cadherin expression in 26 cases (luminal A subtype – nine cases, luminal B subtype – five cases, HER2 subtype – three cases, basal-like subtype – seven cases, unclassified subtype – two cases), and a weak positive one in 16 cases (luminal A subtype – six cases, luminal B subtype – eight cases, HER2 subtype – one case, basal-like subtype – one case). The statistical analysis revealed significantly statistical differences between E-cadherin and tumoral grade ($p=0.0208$), histological subtype ($p=0.0081$), triple negative molecular subtypes and non-triple negative, respectively ($p=0.0361$). These findings support the potential value of E-cadherin for a supplementary differentiation of molecular subtypes, based on the biological significance of its capacity of expression.

Keywords: E-cadherin, breast cancer, molecular classification.

Introduction

The molecular classification of breast cancer [1] resulted in major changes in the approach of breast tumoral pathology, from diagnosis to treatment. A real avalanche of studies brings numerous arguments for the definition of the tumoral molecular types and subtypes by the use of "surrogate" markers. However, despite the numerous demonstrated data, the molecular classification is still a perfectible tool [2]. This consideration is supported both by heterogeneous reports in the mainstream publication and by constant objectives of researchers focused on breast cancer diagnosis refinement by implementation of supplementary molecular markers which might differentiate specific biological behaviors reflected into a personalized therapy.

E-cadherins, beside claudins, are epithelial morphological stabilizers, performing complex functions as receptors, providers of cellular and tissular structural integrity, and functional interactive mediators [3].

E-cadherins modulate the invasive mechanisms either by individual participation, either by association with members of the cadherins family, acting by simple organization/distribution or involvement in variable signaling pathways [3]. Six cadherins classes have been identified (type I, type II, type III, "Fat and Daschous", protocadherins, desmosomal cadherins), codified by 13 specific genes (CDH1, CDH2, CDH3, CDH4, CDH5, CDH11, CDH13, CDH15, FAT4, PCDH8, PCDH8, DSG2, and DSG3) corresponding to the members of each class [4].

E-cadherins have a transmembrane glycoprotein structure with three distinctive domains: intracytoplasmic, transmembrane, and extracellular, respectively. The cytoplasmic domain perform a double role, of junctional/structural proteins (by association to γ and β p120 providing the binding to the actinic cytoskeleton and contributing to cellular architectural organization) and of signal transducer [4]. The extracellular domain (EC) is composed of four subdomains: EC-1 (calcium-dependent),

EC-2, EC-3, EC-4 (adherent subdomains) adjacent to the membrane proximal extracellular domain [5].

Both *in vivo* and *in vitro* studies demonstrate the suppressor tumoral gene function of E-cadherins [6]. E-cadherins inhibit Wnt pathways, remove EGFR recycling, and prevent FGF internalization [7, 8], as involvement in motility and invasion regulation. Thus, any genic abnormality followed by structural changes would inhibit carcinogenic sequences, mainly the tumoral progression.

As an interesting finding, any cadherin type associated to above-mentioned genes is represented in breast structure either in a physiological status (luminal, ductal, and alveolar epithelium, mesenchymal cells and stroma, myoepithelial cells, muscle and nervous elements), or either pathological tumoral status [3].

E-cadherin involvement in mammary gland is reported starting with the embryonic life (when it is involved in epithelial tubulogenesis) and progressing to healing and tumoral progression processes related to E-cadherins ability to change their phenotype from epithelial to mesenchymal features. Thus, E-cadherins are key elements in the epithelial–mesenchymal transition mechanism (providing cellular mobility and invasion) and in mesenchymal–epithelial one respectively (providing extravasation and migration) [9]. The *in vivo* studies of E-cadherins have mainly been focused on epithelial–mesenchymal and mesenchymal–epithelial transitions as basic processes in breast tumoral pathology involving signaling pathways that regulate “cadherinic switch” toward tumor benefit [10, 11]. The epithelial–mesenchymal transition is facilitated either by loss of E-cadherins expressions, either by the amplification of expression and mutations of E-cadherins inhibitors (*e.g.*, Snail transcription factors family, as Snail1 and Slug, Zeb family, namely Zeb1 and Zeb2, Twist family, and E12/47 family) eventually resulting in tumor invasion promotion [10, 12, 13].

The loss of E-cadherins in breast pathology may be also attributed to genomic alterations resulted from mutations accumulation in CDH1 cadherinic genes, located on 16q22.1 chromosome [14, 15], transcriptional regulation changes, CpG promoters hypermethylation, promoters or non-coding RNA methylation [16–18].

On the bases of the above considerations, the objectives of our study were: (i) investigation of E-cadherin profile in breast cancer operational molecular subtypes aiming the identification of expression differences; (ii) analysis of possible correlations between E-cadherin and specific clinicopathological and molecular characteristics.

Materials and Methods

Case selection

Our group of study comprised 42 cases of breast cancers, diagnosed between 1st of January 2006 and 31st of December 2011, in “Elena Doamna” Obstetrics and Gynecology University Hospital of Iassy, Romania.

The study has been approved by the Ethics Committee of the “Grigore T. Popa” University of Medicine and Pharmacy of Iassy, based on patients’ informed consent.

The clinicopathological features of the patients included in our study are briefly illustrated in Table 1.

Table 1 – Synopsis of clinicopathological characteristics of the studied group

Clinicopathological characteristics	Cases	
	No.	%
Age [years]		
≤55	14	33.33
>55	28	66.66
Histological types		
Ductal invasive carcinoma	26	61.9
Lobular invasive carcinoma	7	16.66
Miscellaneous histological subtypes:	9	21.42
Medullary carcinoma	1	2.38
Tubular carcinoma	1	2.38
Mucinous carcinoma	1	2.38
Apocrine carcinoma	1	2.38
Mixed carcinoma	5	11.9
Stage T		
I	9	21.42
II	23	54.76
III	7	16.66
IV	3	7.14
Stage N		
Nx	4	9.52
N0	14	33.33
N1	17	40.47
N2/N3	7	16.66
Stage M		
Mx	39	92.85
M0	2	4.76
M1	1	2.38
Degree of differentiation		
G1 (well differentiated)	12	28.57
G2 (moderately differentiated)	17	40.47
G3 (poorly differentiated)	13	30.95

As a specific morphological profile, the five cases classified as mixed carcinoma included ductal invasive carcinoma and ducto-lobular carcinoma association, in two cases, cribriform carcinoma, in two cases, and mucinous carcinoma in a case. The differentiation degrees evaluation used the Scarff–Bloom–Richardson classification criteria [19], related to tubules formation, nuclear grade, and mitotic status.

Immunohistochemistry

The studied group has been investigated by immunohistochemistry using an antibody panel, which permitted a diagnosis in correlation to molecular classification, and E-cadherin evaluation (Table 2).

Table 2 – Main characteristics of used antibodies

Antibody	Clone, source	Dilution	Expression
ER	1D5, DakoCytomation, CA, USA	Ready-to-use	Nuclear
PR	PgR636, DakoCytomation, CA, USA	Ready-to-use	Nuclear

Antibody	Clone, source	Dilution	Expression
Her2/neu	c-ERB B2, DakoCytomation, CA, USA	Ready-to-use	Membranar
CK5/6	D5/16B4, DakoCytomation, CA, USA	1:75	Cytoplasmic
EGFR	EGFR PharmDx Kit, DakoCytomation, CA, USA	Ready-to-use	Membranar
E-cadherin	NCH38, DakoCytomation, Denmark	1:75	Membranar

HIER technique using an antigen retrieval solution with pH 6 was applied to the whole panel of antibody, followed by the standard phases of the working protocol, automatically performed (Dako Autostainer Plus, Dako Cytomation, Glostrup, Denmark).

Semi-quantitative assessment

E-cadherin immunohistochemical reaction was semi-quantitatively evaluated, using a scoring system [20] as a correlation of positive cells percentage with the staining intensity, as following: 0 – lack of staining or membrane positivity in <10% of tumoral cells, 1 – incomplete and weak membrane staining in >10% of tumoral cells, 2 – complete membrane staining, of weak or moderate intensity in >10% of tumoral cells, and 3 – complete, strong membrane staining in >10% of tumoral cells. According to this score, the reaction is considered as negative for 0 and 1 scores, weak positive for score 2, and strong positive for score 3.

Statistical analysis

Statistical analysis has been performed using SPSS 13.0 program, by applying Pearson test, as the most used type of χ^2 significance test, based on columns and rows association of a table with two entries, cross frequencies regarding discrete or discretized variables. The Yates correction (also known as the continuity corrected *chi-square*) was applied due to the relatively small dimensions of the study group, in the cases of the cells with less than five elements. Through the Yates correction we can obtain a better approximation of the binomial distribution and the result is conservatory *i.e.* the significance is acquired harder than with the direct application of the χ^2 test. The statistical significance was interpreted according to the standard, for $p < 0.05$.

Results

E-cadherins profile evaluation, illustrated by membrane positivity, revealed a strong positivity in 26 cases and a weak positivity in 16 cases. No negative case was registered.

E-cadherin positive expression was characterized by immunoreaction strong positivity, in 90–100% of tumoral cells in 20 cases and in 50%, 70%, 75%, and 80% of remnant six cases, respectively.

The cases revealing a low positivity showed a weak and moderate intensity of immunohistochemical reaction, with a 20–80% of positive tumoral cells.

According to the molecular subtypes, cases distribution was the following:

- E-cadherin strong positive expression: luminal A subtype – nine cases, luminal B subtype – five cases, HER2 subtype – three cases, basal-like subtype – seven cases, unclassified subtype – two cases;

- E-cadherin weak positive expression: luminal A subtype – six cases, luminal B subtype – eight cases, HER2 subtype – one case, basal-like subtype – one case.

Considering the luminal A, luminal B, and HER2 subtypes as belonging to the non-triple negative category and the basal-like and unclassified subtypes as belonging to the triple negative category, E-cadherin distribution was the following:

- Non-triple negative category, E-cadherin strong positive – 17 cases;
- Non-triple negative category, E-cadherin weak positive – 15 cases;
- Triple negative category, E-cadherin strong positive – nine cases;
- Triple negative category, E-cadherin weak positive – one case.

According to the data obtained by semi-quantitative evaluation, the weak positive E-cadherin expression was not registered in unclassified subtype.

Both the results obtained in semi-quantitative evaluation of each case and the correlations with molecular subtypes are presented in detail in Table 3.

Table 3 – E-cadherin expression in different molecular subtype of breast carcinoma

Case No.	Percentage of positive cells	Reaction intensity	Score	Reaction interpretation	Molecular subtype
1.	20%	Weak	2	Weak expression	Luminal B
2.	100%	Strong	3	Strong expression	Basal-like
3.	100%	Strong	3	Strong expression	Luminal A
4.	100%	Strong	3	Strong expression	Luminal A
5.	30%	Moderate	2	Weak expression	Luminal B
6.	75%	Moderate	2	Weak expression	Luminal B
7.	90%	Moderate	2	Weak expression	Luminal A
8.	90%	Strong	3	Strong expression	Luminal A
9.	80%	Strong	3	Strong expression	Luminal B
10.	100%	Strong	3	Strong expression	HER2
11.	100%	Strong	3	Strong expression	Luminal A
12.	80%	Moderate	2	Weak expression	Luminal B
13.	100%	Strong	3	Strong expression	Luminal A
14.	100%	Strong	3	Strong expression	Luminal B
15.	100%	Strong	3	Strong expression	Luminal A
16.	50%	Moderate	2	Weak expression	Luminal B
17.	100%	Strong	3	Strong expression	Luminal B
18.	30%	Moderate	2	Weak expression	HER2
19.	100%	Strong	3	Strong expression	Luminal B
20.	40%	Weak	2	Weak expression	Luminal B
21.	100%	Strong	3	Strong expression	Luminal B

Case No.	Percentage of positive cells	Reaction intensity	Score	Reaction interpretation	Molecular subtype
22.	70%	Moderate	2	Weak expression	Luminal B
23.	60%	Moderate	2	Weak expression	Luminal A
24.	100%	Strong	3	Strong expression	Unclassified
25.	50%	Moderate	2	Weak expression	Luminal A
26.	20%	Moderate	2	Weak expression	Basal-like
27.	95%	Strong	3	Strong expression	Basal-like
28.	75%	Strong	3	Strong expression	Unclassified
29.	50%	Strong	3	Strong expression	Luminal A
30.	100%	Strong	3	Strong expression	HER2
31.	100%	Strong	3	Strong expression	Luminal A
32.	100%	Strong	3	Strong expression	Basal-like
33.	70%	Strong	3	Strong expression	Basal-like
34.	100%	Strong	3	Strong expression	Basal-like
35.	100%	Strong	3	Strong expression	Luminal A
36.	40%	Weak	2	Weak expression	Luminal A

Case No.	Percentage of positive cells	Reaction intensity	Score	Reaction interpretation	Molecular subtype
37.	90%	Strong	3	Strong expression	Basal-like
38.	100%	Strong	3	Strong expression	HER2
39.	50%	Weak	2	Weak expression	Luminal A
40.	25%	Weak	2	Weak expression	Luminal B
41.	100%	Strong	3	Strong expression	Basal-like
42.	100%	Weak	2	Weak expression	Luminal A

Figures 1–5 are illustrating the strong immunohistochemical expression of E-cadherin.

The statistical analysis between E-cadherin expression (strong and weak, respectively), clinicopathological parameters, and tumoral stage revealed the absence of any significant statistical differences. However, correlations were noted between E-cadherin and tumoral grade ($p=0.0208$) (Table 4), and E-cadherin and histological subtype ($p=0.0081$) (Table 4).

Significantly statistical differences have been also registered for E-cadherin expression correlated to triple negative molecular subtypes and non-triple negative, respectively ($p=0.0361$) (Table 4).

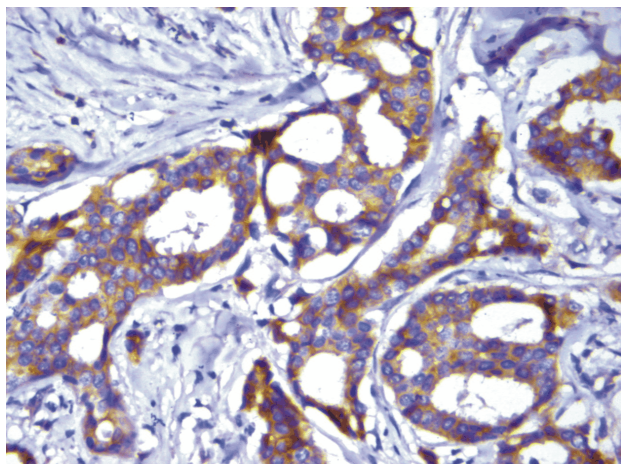


Figure 1 – Breast carcinoma, luminal A subtype, strong E-cadherin expression (IHC, ×400).

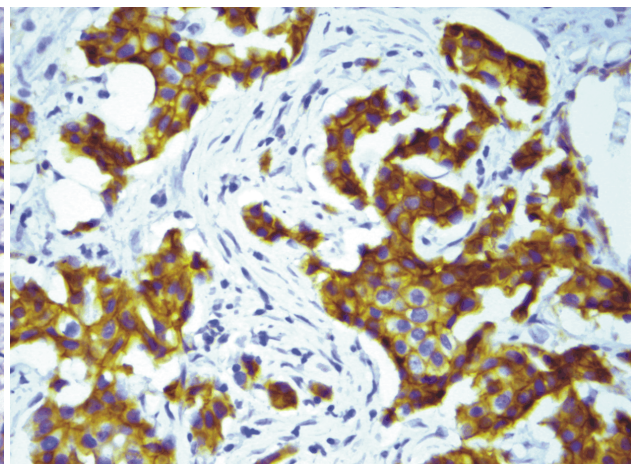


Figure 2 – Breast carcinoma, luminal B subtype, strong E-cadherin expression (IHC, ×400).

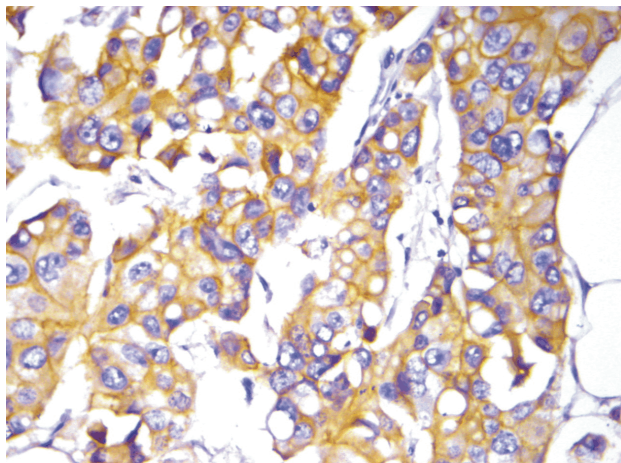


Figure 3 – Breast carcinoma, HER2 subtype, strong E-cadherin expression (IHC, ×400).

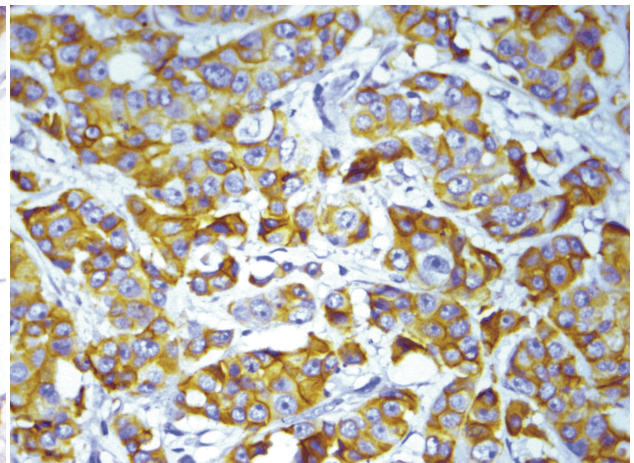


Figure 4 – Breast carcinoma, basal-like subtype, strong E-cadherin expression (IHC, ×400).

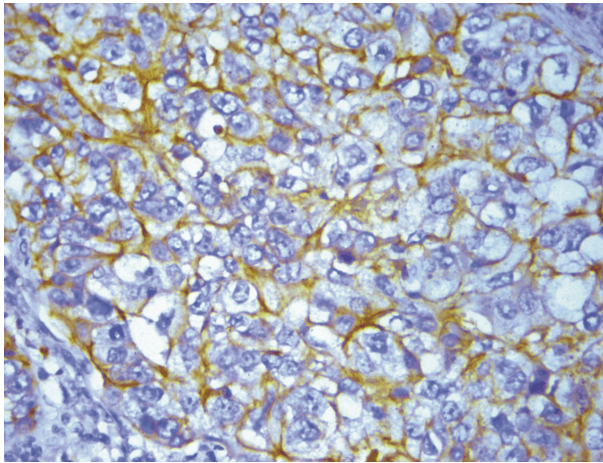


Figure 5 – Breast carcinoma, unclassified subtype, strong E-cadherin expression (IHC, $\times 400$).

Table 4 – Contingency table (chi-square test, χ^2) related to E-cadherin expression

Clinicopathological parameters	E-cadherin expression					Total Cases (42)
	Strong		Weak		P-value	
	Cases (26)		Cases (16)			
	No.	%	No.	%		
Age [years]						0.2613
≤55	7	50	7	50	14	
>55	19	67.85	9	32.14	28	
Tumoral stage						0.5423
I	5	55.55	4	44.44	9	
II	13	56.53	10	43.47	23	
III	6	85.72	1	14.28	7	
IV	2	66.66	1	33.33	3	
Tumoral stage						0.1770
I + II	18	56.25	14	43.75	32	
III + IV	8	80	2	20	10	
Tumoral grade						0.0208
1	9	75	3	25	12	
2	13	76.47	4	23.53	17	
3	4	30.77	9	69.23	13	
Morphologic subtype						0.0081
Ductal invasive carcinoma	17	65.38	9	34.62	26	
Lobular invasive carcinoma	1	14.28	6	85.72	7	
Miscellaneous histological subtypes	8	88.88	1	11.11	9	
Molecular subtype						0.0361
Triple negative	9	90	1	10	10	
Non-triple negative	17	53.12	15	46.88	32	

Discussion

E-cadherins are members of the cadherins superfamily, exhibiting a decisional role in cellular polarization maintenance and in tissular homeostasis regulation [3]. As transmembrane integral glycoproteins with complex and incompletely deciphered functions, E-cadherins are involved in the mediation of carcinogenesis specific biological processes, by their capacity to preserve the junctional structural capacity and to control the expression of numerous signals involved in malignant transformation sequences [3].

Structural and functional unbalance initiated due to E-cadherin expression loss results in direct effects on cellular invasion and proliferation. E-cadherins act as tumoral suppressor proteins by their ability to block not only the uncontrolled proliferation but also the cellular differentiation toward a malignant phenotype [3]. Consequently, complete or partial involvement of E-cadherin expression participates in invasion and metastasis [3].

E-cadherin prognosis significance in cancer, including the breast cancer, has been intensely studied and the data concerning the correlation between E-cadherin expression versus prognosis are inconstant.

Unfavorable prognosis significance of the loss of E-cadherin expression has been demonstrated in different studies [21, 22]. Thus, its absence is frequently associated to large tumor size, metastatic lymph node status, local or regional tumoral recurrence, low grade of differentiation, advanced tumoral stage, and triple negative subtypes [6, 23]. Recently, E-cadherin has been considered as an independent prognosis marker of triple negative breast cancer [24]. However, there is data that confirm the association of an increased expression of E-cadherin with an unfavorable prognosis and short-term survival [25]. However, no significant correlation between E-cadherin expression and patient evolution has been found by other researchers [26].

Our results demonstrated an increased E-cadherin expression in 26 cases of the total 42 cases (61.6%) included in our study group as compared to 16 cases (38.09%) which had a weak E-cadherin expression. The statistical analysis showed a correlation between E-cadherin and tumoral grade ($p=0.0208$). A special focus on the significance of our results as a valuable indicator of the E-cadherin decreased expression correlated to the tumoral grade enhancement should be placed. Specifically, nine of the 16 cases (69.23%) showing a weak E-cadherin expression corresponded to grade 3 of differentiation.

The literature data depict E-cadherin gene (CDH1) mutations associated to a weak or absent expression mainly in infiltrative lobular carcinomas, disregarding the tumoral stage or clinical evolution [27–29]. E-cadherin weak expression associated to lobular invasive subtype noticed in our study are similar to literature reports. This observation was based on the correlation analysis showing statistically significant differences between E-cadherin and histological subtypes ($p=0.0081$), as six of a total of seven cases (85.72%) histopathologically diagnosed as invasive lobular carcinomas were characterized by weak E-cadherin expression.

The weak E-cadherin expression may explain the morphological phenomena of invasive lobular carcinoma, showing a characteristic tumoral pattern different from that of invasive ductal carcinoma. Concomitantly, a special emphasis should be addressed to the loss of CDH1 heterozygosity in ductal type carcinomas, without accumulation of CDH1 allelic mutations [30]. This observation may partially explain the E-cadherin expression preservation in non-lobular histopathological category. According to this information, an focus on the histopathological profile showed a strong expression of E-cadherin in 17 of a total of 26 cases (63.38%) classified

as ductal invasive carcinoma and in eight of nine cases (88.88%) diagnosed as mixed type, based on the association of ductal invasive carcinoma histological type with cribriform, tubular, and mucinous types.

Our results are contradictory to the recent literature reports regarding the molecular classification [24], indicating a correlation between E-cadherin loss, triple negative molecular category and, consequently, poor prognosis. In the investigated group, within the triple negative category, E-cadherin strong expression was dominant (nine of 10 cases). However, statistical evaluation resulted in statistically significant differences ($p=0.0361$) in E-cadherin comparative analysis of strong and weak expression, respectively and non-triple negative and triple negative category, respectively. We consider this disaccord justified by the configuration of the study group, which comprised a relatively reduced number of cases.

Conclusions

Consequently, we support E-cadherin potential value for a supplementary differentiation of molecular subtypes, based on the biological significance of its capacity of expression and we expect further confirmation in larger study groups.

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References

- Perou CM, Sørli T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO, Botstein D, *Molecular portraits of human breast tumours*, Nature, 2000, 406(6797):747–752.
- Hergueta-Redondo M, Palacios J, Cano A, Moreno-Bueno G, *"New" molecular taxonomy in breast cancer*, Clin Transl Oncol, 2008, 10(2):777–785.
- Andrews JL, Kim AC, Hens JR, *The role and function of cadherins in the mammary gland*, Breast Cancer Res, 2012, 14(1):203–213.
- Nelson WJ, *Regulation of cell–cell adhesion by the cadherin–catenin complex*, Biochem Soc Trans, 2008, 36(Pt 2):149–155.
- Gumbiner BM, *Regulation of cadherin-mediated adhesion in morphogenesis*, Nat Rev Mol Cell Biol, 2005, 6(8):622–634.
- Gould Rothberg BE, Bracken MB, *E-cadherin immunohistochemical expression as a prognostic factor in infiltrating ductal carcinoma of the breast: a systematic review and meta-analysis*, Breast Cancer Res Treat, 2006, 100(2):139–148.
- Fedor-Chaikin M, Hein PW, Stewart JC, Brackenbury R, Kinch MS, *E-cadherin binding modulates EGF receptor activation*, Cell Commun Adhes, 2003, 10(2):105–118.
- Wheelock MJ, Johnson KR, *Cadherin-mediated cellular signaling*, Curr Opin Cell Biol, 2003, 15(5):509–514.
- Chao YL, Shepard CR, Wells A, *Breast carcinoma cells re-express E-cadherin during mesenchymal to epithelial reverting transition*, Mol Cancer, 2010, 9:179.
- Hajra KM, Chen DY, Fearon ER, *The SLUG zinc-finger protein represses E-cadherin in breast cancer*, Cancer Res, 2002, 62(6):1613–1618.
- Cavallaro U, Schaffhauser B, Christofori G, *Cadherins and the tumour progression: is it all in a switch?* Cancer Lett, 2002, 176(2):123–128.
- Adachi Y, Takeuchi T, Nagayama T, Ohtsuki Y, Furihata M, *Zeb1-mediated T-cadherin repression increases the invasive potential of gallbladder cancer*, FEBS Lett, 2009, 583(2):430–436.
- Schmalhofer O, Brabletz S, Brabletz T, *E-cadherin, beta-catenin, and ZEB1 in malignant progression of cancer*, Cancer Metastasis Rev, 2009, 28(1–2):151–166.
- Cleton-Jansen AM, Moerland EW, Kuipers-Dijkshoorn NJ, Callen DF, Sutherland GR, Hansen B, Devilee P, Cornelisse CJ, *At least two different regions are involved in allelic imbalance on chromosome arm 16q in breast cancer*, Genes Chromosomes Cancer, 1994, 9(2):101–107.
- Cool M, Jolicoeur P, *Elevated frequency of loss of heterozygosity in mammary tumors arising in mouse mammary tumor virus/neu transgenic mice*, Cancer Res, 1999, 59(10):2438–2444.
- Lynch HT, Grady W, Lynch JF, Tsuchiya KD, Wiesner G, Markowitz SD, *E-cadherin mutation-based genetic counseling and hereditary diffuse gastric carcinoma*, Cancer Genet Cytogenet, 2000, 122(1):1–6.
- Peinado H, Portillo F, Cano A, *Transcriptional regulation of cadherins during development and carcinogenesis*, Int J Dev Biol, 2004, 48(5–6):365–375.
- Tryndyak VP, Beland FA, Pogribny IP, *E-cadherin transcriptional down-regulation by epigenetic and microRNA-200 family alterations is related to mesenchymal and drug-resistant phenotypes in human breast cancer cells*, Int J Cancer, 2010, 126(11):2575–2583.
- Elston CW, Ellis IO, *Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up*, Histopathology, 1991, 19(5):403–410.
- Qureshi HS, Linden MD, Divine G, Raju UB, *E-cadherin status in breast cancer correlates with histologic type but does not correlate with established prognostic parameters*, Am J Clin Pathol, 2006, 125(3):377–385.
- Gillett CE, Miles DW, Ryder K, Skilton D, Liebman RD, Springall RJ, Barnes DM, Hanby AM, *Retention of the expression of E-cadherin and catenins is associated with shorter survival in grade III ductal carcinoma of the breast*, J Pathol, 2001, 193(4):433–441.
- Goldstein NS, *Does the level of E-cadherin expression correlate with the primary breast carcinoma infiltration pattern and type of systemic metastases?* Am J Clin Pathol, 2002, 118(3):425–434.
- Rakha EA, Abd El Rehim D, Pinder SE, Lewis SA, Ellis IO, *E-cadherin expression in invasive non-lobular carcinoma of the breast and its prognostic significance*, Histopathology, 2005, 46(6):685–693.
- Tang D, Xu S, Zhang Q, Zhao W, *The expression and clinical significance of the androgen receptor and E-cadherin in triple-negative breast cancer*, Med Oncol, 2012, 29(2):526–533.
- Tan DS, Potts HW, Leong AC, Gillett CE, Skilton D, Harris WH, Liebmann RD, Hanby AM, *The biological and prognostic significance of cell polarity and E-cadherin in grade I infiltrating ductal carcinoma of the breast*, J Pathol, 1999, 189(1):20–27.
- Parker C, Rampaul RS, Pinder SE, Bell JA, Wencyk PM, Blamey RW, Nicholson RI, Robertson JF, *E-cadherin as a prognostic indicator in primary breast cancer*, Br J Cancer, 2001, 85(12):1958–1963.
- Sanrió D, Pérez-Mies B, Hardisson D, Moreno-Bueno G, Suárez A, Cano A, Martín-Pérez J, Gamallo C, Palacios J, *Cytoplasmic localization of p120ctn and E-cadherin loss characterize lobular breast carcinoma from preinvasive to metastatic lesions*, Oncogene, 2004, 23(19):3272–3282.
- Mahler-Araujo B, Savage K, Parry S, Reis-Filho JS, *Reduction of E-cadherin expression is associated with non-lobular breast carcinomas of basal-like and triple negative phenotype*, J Clin Pathol, 2008, 61(5):615–620.

- [29] Baranwal S, Alahari SK, *Molecular mechanisms controlling E-cadherin expression in breast cancer*, Biochem Biophys Res Commun, 2009, 384(1):6–11.
- [30] Cleton-Jansen AM, *E-cadherin and loss of heterozygosity at chromosome 16 in breast carcinogenesis: different genetic pathways in ductal and lobular breast cancer?* Breast Cancer Res, 2002, 4(1):5–8.

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