ORIGINAL ARTICLE

Annals of Agricultural and Environmental Medicine 2012, Vol 19, No 3, 541-546
www.aaem.pl

Evaluation of prognostic parameters of E-cadherin status in breast cancer treatment

Anna Brzozowska[1], Tomasz Sodolski[2], Dariusz Duma[3], Tomasz Mazurkiewicz[4], Maria Mazurkiewicz[1]

[1] *Department of Oncology, Medical University in Lublin, Poland*
[2] *Cardiology Department, Medical University in Lublin, Poland*
[3] *Department of Laboratory Diagnostic, Medical University in Lublin, Poland*
[4] *Orthopedics and Traumatology Department, Medical University in Lublin, Poland*

Brzozowska A, Sodolski T, Duma D, Mazurkiewicz T, Mazurkiewicz M. Evaluation of prognostic parameters of E-cadherin status in breast cancer treatment. Ann Agric Environ Med. 2012; 19(3): 541-546.

Abstract

Introduction and objective. Breast cancer is one of the most frequent malignancies in women. Axillary lymph node involvement, tumour size, receptor status, and level of malignancy are the most significant prognostic factors in breast cancer, but insufficient to date. More factors are needed for establishing the prognosis and treatment in these patients. The aim of the presented study was evaluation of E- cadherin expression and its prognostic value among 89 specimens of breast cancer.

Materials and methods. 89 formalin-fixed and paraffin-embedded breast cancer specimens were studied for expression of E-cadherin detected by immunohistochemistry. During 10-year observation overall/OS/and disease-free survival/DFS/ of patients were assessed.

Results. Average of OS and DFS were shorter among patients without expression of E-cadherin in comparison to survival time of patients with expression of E-cadherin.
The lack of E-cadherin expression was present more often among patients with distant metastasis. No essential changes were noticed in the level of E-cadherin depending on the size of the tumour, G, presence of metastasis into the lymph nodes, ER, PR and HER-2, hormonal condition and presence of cancerous tissues in lymphatic vessels and the infiltration of lymph nodes capsules.

Conclusions. E-cadherin may play an important role in the prognosis of breast cancer patients.

Key words

Breast cancer, prognosis, E-cadherin

INTRODUCTION AND OBJECTIVE

For many years breast cancer has been the most common type of tumour among women. Despite significant developments seen in diagnostic as well as improvement in the early recognition and intensive treatment, every fourth women suffering from breast cancer dies because of progression of the illness [1]. The mechanism of progression, especially metastatic, is not completely recognized. Researches in the field of molecular pathology, lasting for many years, indicate the crucial involvement of one of the adhesive protein-cadherins in the development of the disease.

There are about 30 types of glikoprotein in this group. They consist of two main parts: intermembrane and extracellural. In correct conditions, the extra cellular part of cadherin, via the ions of calcium essential for creation of the connection, influences through catenin with similar molecules on neighbouring cell. In this way they create an adhesive complex which maintains cells in compact connection [2].

The main function of classical cadherins N-neuronal, E-epitelial and P-placental is to maintain tissue continuity, to convey intercellular signals and cells movement which enables regulation of processes such as healing of wounds, apoptosis, immunological reactions or migration of leukocytes [3].

In the case of the cancerous process, adhesive proteins play a crucial role in the process of regional invasion, in migration of cancerous cells, and additionally in later maintenance in the remote organs [4, 5]. In the first two processes, it results in the reduction of the amount of cadherin, the result of which is disorder in the transition of intracellular signals, and loosening of intercellular connections [6, 7]. This leads to increased cells invasiveness and ability to migrate [7, 8, 9, 10, 11]. In the process of the development of cancerous cells in healthy tissue there is a new augmentation of E-cadherin expression which enables the stable settling and further development of cells [5].

Much data confirm the statement that diminished E-cadherin expression is observed among patients suffering from: breast, lung, prostate and stomach cancer [12, 13, 14, 15], and this correlates with histological grading/reduced variations/of cancer, more common presence of distant metastasis, and worse prognosis [16, 17].

The results estimating the value of E-cadherin in patients with breast cancer remain contradictory. In most of them, however, it was proved that the loss of E-cadherin expression was a detrimental prognostic factor [18, 19, 20, 21], and most often it was connected with a higher level of

Address for correspondence: Anna Brzozowska Department of Oncology, Medical University in Lublin, Jaczewskiego 7, 20-090 Lublin, Poland.
E-mail: annabrzo@poczta.onet.pl

Received: 20 October 2011; accepted: 29 December 2011

malignancy, presence of metastasis in axillary lymph nodes, lack of estrogen and progesteron receptors, and presence of recurrence [22, 23, 24, 25].

Despite numerous controversies described in the literature, the loss of E-cadherin expression in tumours, including patients suffering from breast cancer, is probably a very important prognostic factor.

The aim of the presented study was evaluation of E-cadherin expression in post-surgical tissue in patients suffering from breast cancer. Dependence of E-cadherin from classical prognostic factors was analysed. The influence of E-cadherin generally and the disease-free survival time of the patients was also evaluated.

MATERIAL AND METHODS

Patients. 89 cases of radically treated breast cancer were selected for the study in Oncology Centre in Lublin during 1995-1996, and the patients participated in the research. All the female patients had undergone radical mastectomy. In 83 patients, no adjuvant treatment was applied. 30 patients were treated with chemotherapy according to CMF scheme and 6 were treated with chemotherapy according to FAC scheme. After chemotherapy, 16 of these patients were additionally treated with hormonotherapy with antiestrogenes. 47 patients were treated only with hormonotherapy with tamoxifen. Adjuvant radiotherapy was applied in 15 patients. All female patients were examined during check-up visits in the Oncology Centre in Lublin. Duration of the observation lasted from 6 months to 10 years. The study population is presented in Table 1.

Table 1. Study population

Factors	No. of patients
Age	average 58.1 +/- 12.5 years
Menopausal condition	
Pre-menopausal	16
Post-menopausal	73
Histopathological subtype	
ductal carcinoma	63
lobular carcinoma	10
tubular carcinoma	2
Rother	14
Malignancy level according to Bloom-Richardson	
G1	10
G2	51
G3	20
Size of the tumor	
T1	28
T2	53
T3	8
Presence of mestastasis into axillary lYmph nodes	
present	36
absent	53
Presence of cancerous cells in blood vessels	
yes	2
no	87
Presence of cancerous cells in lymphatic vessels	
yes	7
no	82
Cancerous infiltration of capsula of axillary lymph nodes	
yes	11
no	78
Expression of estrogen receptor (ER)	
present	67
absent	22
Expression of progesteron receptor (PR)	
present	57
absent	32
Expression of HER-2 receptor	
present	63
absent	26

Immunohistochemistry. The expression of E-cadherin was marked with immunohistochemical staining. In the research, sets produced by the DAKO company were used to mark E-cadherin. The tissue removed from the tumor during the breast cancer operation was cut into pieces and were kept in an incubator at a temperature of 60°C for approximately 12 hours. The microscopic sections were paraffined in xylene and then placed into several strengths of alcohol: 100%, 96%, and 70% with distilled water. The antigen uncovered was diluted with 1:10 Target Retrieval Solution in a container which was placed in water baths at temperatures 95-99°C. Next, in the buffer solution a t the temperature of 95°C, the preparations were placed into and kept in incubators for approximately 20 minutes. The preparations were cooled for approximately 20 minutes and then were rinsed in Tris Buffered Saline (1 sachet was dissolved in a small amount of distilled water and made up to 1,000 ml of distilled water) 3 times for 5 minutes. Peroxidase was blocked by rinsing the preparation in a mixture of 10 ml of prehydrol and 90 ml of distilled water for 5 minutes, and in Tris Buffered Saline for the next 5 minutes. The preparation was then incubated with antibody of E-cadherin for 30 minutes, adding 100 µl for each piece, and rinsed in Tris Buffered Saline 3 times for 5 minutes. Next, the preparations were incubated with HRP for 30 minutes, adding 100 µl for each piece, and rinsed in Tris Buffered Saline 3 times for 5 minutes. A mixture containing 1 ml DAB (3,3 diaminobenzidine) and 1 drop of chromogene was prepared, and the preparations were sprinkled with this mixture. After 5-10 minutes, the mixture was removed from the preparations and rinsed in distilled water. Cell nucleuses were stained with hematoxylin water. The pieces were renewed in increasing strengths of alcohols: 70%, 96%, 100% and xylene.

Evaluation of expression of estrogen and progesterone receptor. The content of ER and PR receptors was evaluated by the immunohistochemical method, using the reaction of ER and PR antibody with the right epitope of the receptor molecule. For this stage of the research, ER and PR 'ER/PR SYSTEM' (DAKO/Code No. K 1900/sets) to mark the receptors were used. The content of the receptors was evaluated on the basis of percentage of stained cancerous cells. The expression of ER and PR receptors was evaluated as positive if it was present in at least 10% of cancerous cells.

Evaluation of expression of HER-2. The immunohistochemical method used consisted in the reaction of polyclonal antibody with receptor HER-2 present in the cellular membrane.

The research was conducted with tests from DAKO (DAKO Hercep-test for Immunoenzymatic Staining, Code No. 5204) according to the procedures advised by the manufacturer. The stained reaction of cellular membranes was evaluated

according to DAKO criteria recommended in 'Atlas for Interpretation of Herceptest Staining'. The result of expression of HER-2 receptor evaluated as 0+, 1+ and 2+ meant the lack of over-expression. The result of 3+ meant the presence of over-expression of HER-2 receptor in the tissue tested.

Evaluation of expression of E-cadherin. The expression was evaluated as positive when E-cadherin was present in at least 70% of examined cells. When the expression was less than 70% in the evaluated cells, in the rest of the preparations it was treated as absent.

Statistical analysis. The method of cross-tabulation tables was used during the statistic analysis of the results. The differences between evaluated groups were examined with chi-square test.

The method of the survival analysis by Kaplan-Meier was used in the evaluation of the survival time. The 10-year disease-free survival was evaluated (from the time of the operation to the appearance of failure) and 10-year overall survival time (from time of the operation to time of death). The Wilcoxon test with Gehan's modification was used in testing the differences between the periods of survival among the examined patients. $P < 0.05$ was considered to be statistically significant.

RESULTS

Positive expression of E-cadherin was present in 67 patients (75.3%). The loss of expression of E-cadherin was typical for patients who during the observation had distant metastasis. The examination proved that the loss of expression of E-cadherin was present slightly more often in patients with a high level of malignancy tumours/G3/and with presence of metastasis to the axillary lymph nodes. This dependence, however, was not essential statistically. The loss of expression of E-cadherin was visible in 50% of the patients with lobular cancer. In the rest of the patients, the expression of E-cadherin was confirmed in 80% of those examined. It was not noted whether the hormonal condition of the examined women, size of the tumour, presence of thrombosis from cancerous cells in blood vessels, infiltration of lymph nodes capsule and expression of ER, PR, HER-2 receptors had any influence on the level of the expression of E-cadherin. It was observed that in patients with the presence of cancerous cells in lymphatic nodes, the lack of expression of E-cadherin occurred more often. Due to the small number of patients with cancerous cells present in lymphatic nodes, however, this result is still difficult to interpret (Tab. 2).

Table 2. Presence of expression of E-cadherin dependent on tested prognostic factors

Examined characteristic	Positive expression of E-cadherin No. of patients	Lack of expression of E-cadherin No. of patients/	p
Menopausal condition			>0.05
Pre-menopausal	5	6	
Post-menopausal	43	35	
Histopathological subtype			< 0.05
ductal carcinoma	50	13	
lobular carcinoma	5	5	
tubular carcinoma	2	0	
other	10	4	
Malignancy grade according to Bloom-Richardson:			>0.05
G1	8	2	
G2	37	14	
G3	16	4	
Size of tumour			>0.05
T1	22	6	
T2	40	13	
T3	5	3	
Presence of mestastasis into axillary lymph nodes			>0.05
present	26	10	
absent	41	12	
Presence of cancerous tissue in blood vessels			> 0.05
yes	1	1	
no	66	21	
Presence of cancerous cells in lymphatic vessels			< 0.01
yes	2	5	
no	65	17	
Cancerous infiltration of axillary lymph nodes			>0.05
yes	59	19	
no	8	3	
Expression of estrogen receptor (ER)			>0.05
present	49	18	
absent	18	4	
Expression of progesteron receptor (PR)			>0.05
present	43	14	
absent	24	8	
Expression of HER-2 receptor			>0.05
Present	46	17	
absent	21	5	
Presence of metastatic lesions			<0.05
present	26	15	
absent	41	7	

During the 10-year observation, 20 patients died because of progression of the disease. The total survival time was 6.7 – 120 months. Average – 97.3 months, median – 113.4 months. In 41 patients, the progression of the cancer was present during the observation. Local recurrence was present in 3 patients and distant metastasis were present in the remaining 38. Disease-free survival time was 0.7-120 months. Average – 84.8 months, median – 111.7 months (Fig. 1).

A shorter time of overall as well as disease-free survival time in patients with the loss of the expression of E-cadherin was observed. The overall survival time in patients with the expression of E-cadherin was from 9.6 months to 120 months. Average – 100.4 months, median – 113.4 months. However, in patients with loss of expression of E-cadherin, the overall survival time was shorter and lasted from 6.7 months to 120 months. Average – 87.6 months, median – 115.5 months (Fig. 2).

Disease-free survival time was also shorter in patients without the expression of E-cadherin, compared with other patients. In patients without the expression it was: 0.7 months – 120 months. Average – 71.2 months, median – 76.2 months. In the rest of the patients it was: 0.7 months – 120 months. Average – 89.3 months, median – 112.3 months (Fig. 3).

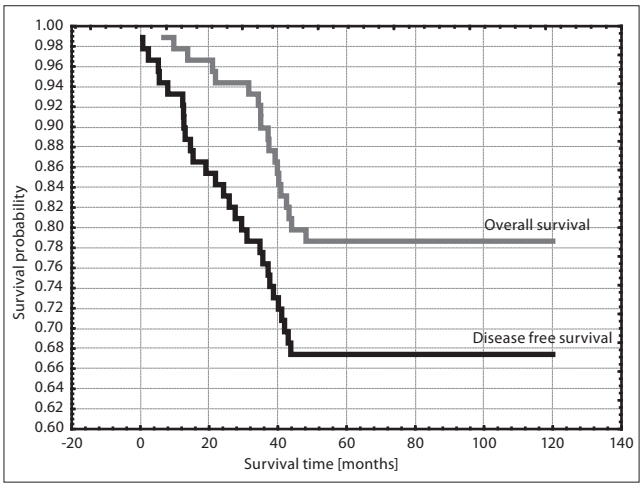

Figure 1. Overall and disease-free survival time in examined patients

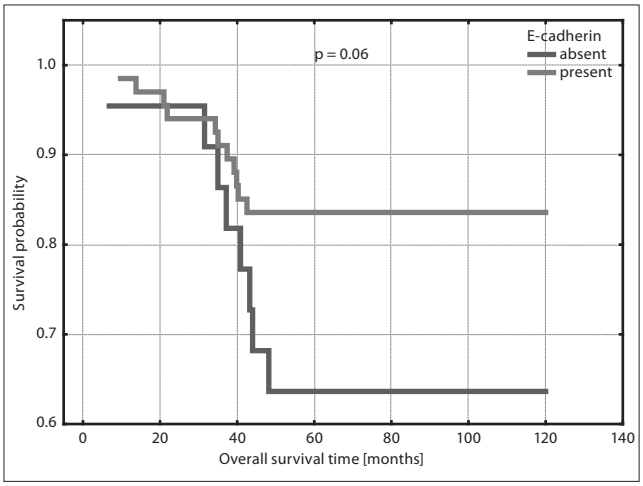

Figure 2. Overall survival time in examined patients depending on expression of E-cadherin

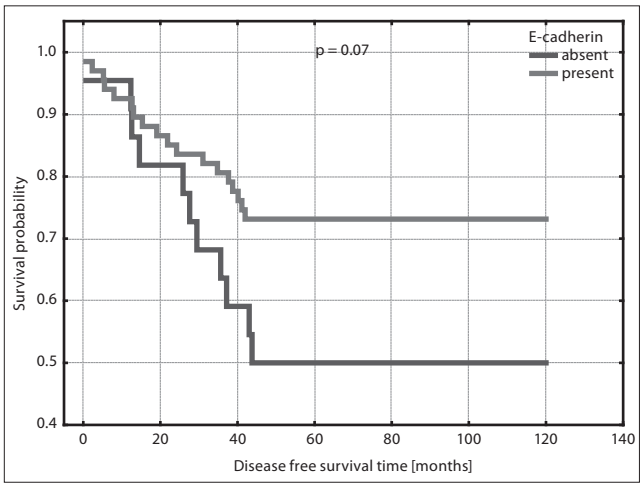

Figure 3. Disease-free survival time in examined patients depending on expression of E-cadherin

DISCUSSION

Ongoing research and experiments interchangeably indicate the enormous role played by E-cadherin in the process of cancer development. It especially influences the stage of metastasis formation. The lack of possibility to use E-cadherin as a prognostic factor in patients suffering from breast cancer is the result of numerous controversies in the manner of its marking in the research, furthermore, there is no straightforward evaluation of its value.

Huge discrepancies relate to the preparation of the material taken for evaluation. A part of the research is conducted with frozen specimens which are more weakly stained, while the major part is conducted on paraffined specimens [23, 24, 26]. This is the reason why in the literature such different results are cited, and the loss of expression of E-cadherin evaluated from 45% – 63% in the case of breast cancer [17, 27]. There is also the fact that cytoplasmic staining is very difficult to interpret, which is observed in some cases of lobular cancer [18]. Even though there is no unequivocal proof, E-cadherin present in cytoplasm remains inactive and should not have any influence on the adhesive properties of the cell [28]. The presence of E-cadherin in cytoplasm of the cell may be caused by defects in the mechanism transporting molecules on the cell surface, or failure of the alpha positioning of cathenin. Most authors, similar to those of this article, do not take into consideration the staining of cytoplasm in their analysis.

The interpretation of received staining is also debatable. In the immunohistochemical method, the major problem is still the subjective evaluation of the pathomorphologists and their experience. There are no synonymously accepted criteria for considering evaluation of the level of the loss of E-cadherin. Most authors, as in the presented study, assume that the correct functioning of the cells requires the presence of E-cadherin in at least 70% of stained cells. Its expression in less than 70% of evaluated cells is treated as the lack of E-cadherin [29, 30]. In the literature, there is also the fact that there are many evaluation scales of expression of E-cadherin. Some of them take into account immensity as well as the intensity of cells staining, each evaluated separately in 3 or 4 ranges [31, 32, 33]. Batistatou et al. took into account the simple division of the expression of E-cadherin. Its presence was defined as staining at least 50% of the cells; its lack defined if the number of the cells were less than 50% [16].

The interpretation of received results is also made difficult because the loss of E-cadherin is seen more often, and additionally, some authors claim that it is present in almost all cases of lobular cancers [24, 26, 28]. This is the reason why separate analysis of histopathological cancer is more and more often common. In the presented research the loss of E-cadherin was observed in 50% of the patients with lobular cancer. Because of the small number of patients with this type of disease, further analysis was conducted together with all histopathological cases.

The obtained results indicate that the loss of expression of E-cadherin on the surface of the cell has a great impact on the reduction of overall and disease-free survival time. It indicates greater invasiveness and tumour malignancy. In the examination of 1,665 patients suffering from lobular cancer, Rakh et al. confirmed that the loss of expression of E-cadherin has a crucial influence on the reduction of overall survival time (HR 1.53, 95% CI 1.09, 2.14; p=0.013) and disease-free survival time (HR 1.56, 95% CI 1.23, 1.99; p<0.001) [34]. Similar results have also been frequently obtained in the analysis of the patients suffering from ductal cancer where, together with the loss of expression of E-cadherin, the overall survival and disease-free survival time were shortened [21, 26, 35]. Charpin et al. also observed

a shorter survival time in patients without metastasis to the axillary lymph nodes [18]. The shorter time of overall survival and disease-free survival time in patients without expression of E-cadherin may also be linked with immunity to those cancers to some treatments, as observed by Berezhnay et al. These authors claim that breast cancer cells with proven immunity to cytostatics (cyclophosphamide, doksorubicin, 5-fluorouracil) were characterized by a significantly lower level of expression of E-cadherin than sensitive cells [36].

As many researches have shown, the expression of E-cadherin is vitally smaller in tumours with a higher level of malignancy [17, 21, 23, 24]. This is also confirmed by our research. In the research by Heinmann, 11% of tumours on the level of G1 showed no expression of E-cadherin, on the level of G3 it was 49% [37]. Most researches which confirmed this dependency were performed on frozen specimens. The researches carried out on paraffined specimens, the results are contradictory [26, 30]. Lipponen et al. did not notice any significant differences of expression of E-cadherin dependent on the level of malignancy. Suciu et al. stated that even the percentage of tumours with E-cadherin was higher, together with the level of malignancy [26, 30]. They did not observe E-cadherin expression in G1 tumors; in G2 tumors it was present in 55.5%, and in G3 tumors it was as high as 62.5%. This research was performed in a small group of 22 patients, which makes the interpretation more difficult [30].

In the presented study, as in many articles in the literature, we did not observe any dependency between the level of expression of E-cadherin and such prognostic factors as: size of the tumour, presence of metastasis in axillary lymph nodes, presence of infiltration in lymph node capsules, presence of cells and thrombosis in lymphatics and blood vessels, or expression of estrogen and progesteron receptors and HER-2 [18, 21, 23, 26, 28, 32, 40]. Some authors, however, describe a dependency between the lack of E-cadherin and presence of metastasis in axillary lymph nodes [17, 21], size of the tumour [17, 38], estrogen and progesteron receptors or HER-2 [17, 21, 30, 39].

In the evaluated group of patients in whom during observation there was exposure of distant metastasis, this more often indicated the lack of expression of E-cadherin in the tumour cells. This confirms the theory about the role of E-cadherin as an adhesive molecule the lack of which leads to the spreading of the tumour. Similar results have been obtained by other authors [5, 9, 17] who have proved that the presence of distant metastasis is visible more often in patients with a lowered level of expression of E-cadherin in the primary tumour [5, 9]. There is no confirmation of the causes of this phenomenon anywhere in the literature. The major role is played by disturbances in the functions of all elements of the system of intercellular adhesion with genetic defects.

The significant influence of the level of E-cadherin on reduction of survival time and increased risk of distant metastasis makes it a crucial prognostic factor. The fact that it is easy to evaluate by the immunohistochemical method which, despite numerous controversies and remarks, is still the most available and most usable, will enable its common usage. Because of numerous controversies and the lack of straightforward results relating to its value as a prognostic factor in breast cancer, it still requires much advanced research.

CONCLUSIONS

Results of the analysis in the presented study indicate that a lowered level of E-cadherin in the cells of invasive breast cancer crucially increases the risk of distant metastasis. Moreover, it influences the reduction of overall and disease-free survival time in patients.

REFERENCES

1. Cowin P, Rowlands TM, Hatsell S J, et al. Cadherins and catenins in breast cancer. Curr Opin Cell Biol. 2005; 17: 499-508.
2. Takeichi M. Cadherin cell adhesion receptors as a morphogenetic regulator. Science 1991; 251; 1451-1455.
3. Gumbinger B M. Cell adhesion: the molecular basis of tissue architecture and morphogenesis. Cell 1996; 84, 345-357.
4. Brakebusch C, Bouvard D, Stanchi F. Integrins in invasive growth. J Clin Invest. 2002; 109: 999-1006.
5. Kowalski P J, Rubin M A, Kleer C G. E-cadherin expression in primary carcinomas of the breast and its distant metastases. Breast Cancer Res. 2003; 5 (6): R217-R222.
6. Tang DG, Honn K V. Adhesion molecules and tumor metastasis: an update. Invasion Metastasis. 1995; 14: 109-122.
7. Okegawa T, Pong RC, Li Y, et al. The role of cell adhesion molecule in cancer progression and its application in cancer theraphy. Acta Biochim Pol 2004; 51 (2): 445-457.
8. Ahmad IR, Hart IR. Mechanism of metastasis. Crit Rev Oncol Hematol 1997; 26 (3): 163-173.
9. Jeschke U, Mylonas I, Kuhn C. Expression of E-cadherin in human ductal breast cancer carcinoma in situ, invasive carcinomas, their lymph node metastases, their distant metastases, carcinomas with recurrence and in recurrence. Anticancer Res. 2007; 27 (4A): 1969-1974.
10. Larue L, Ohsugi M, Hirchenhain J, et al. E-cadherin nullmutant embryos fail to form a trophectoderm epithelium. Proc Natl Acad Sci U S A 1994; 91: 8263-8267.
11. Frixen UH, Behrens J, Sachs M, et al. E-cadherin mediatedcell-cell adhesion prevents invasiveness of human carcinoma cells. J Cell Biol. 1991; 113: 173-185.
12. Umbas R, Isaacs WB, Bringuier PP, et al. Decreased E-cadherin expression is associated with poor prognosis in patients with prostate cancer. Cancer Res. 1994; 54: 3929-3933.
13. Umbas R, Isaacs WB, Bringuier PP, et al. Relation between aberrant alpha-catenin expression and loss of E-cadherin function in prostate cancer. Int J Cancer.1997; 74: 374-377.
14. Mayer B, Johnson JP, Leitl F, et al. E-cadherin expression in primary and metastatic gastric cancer: down-regulation correlates with cellular dedifferentiation and glandular disintegration. Cancer Res. 1993; 53: 1690-1695.
15. Dorudi S, Hanby AM, Poulsom R, et al. Level of expression of E-cadherin mRNA in colorectal cancer correlates with clinical outcome. Br J Cancer. 1995; 71: 614-616.
16. A Batistatou, D Peschos, H Tsanou, et al. In breast carcinoma dysadherin expression is correlated with invasiveness but not with E-cadherin. Br J Cancer. 2007; 7;96 (9): 1404-1408.
17. Shiozaki H, Kobayashi K, et al. Expression of E-cadherincell adhesion molecules in human breast cancer tissues and its relationship to metastasis. Cancer Res. 1993; 53: 1696-1701.
18. Charpin C, Garcia S, Bonnier P, et al. Reduced E-cadherin immuno-histochemical expression in node-negative breast carcinomas correlates with 10-year survival. Am J Clin Pathol. 1998; 109: 431-438.
19. Guriec N, Marcellin L, Gairard B, et al. E-cadherin mRNA expression in breast carcinomas correlates with overall and disease-free survival. Invasion Metastasis. 1996; 16: 19-2.
20. Heimann R, Lan F, McBirde R, et al. Separating favorablefrom unfavorable prognostic markers in breast cancer: the role of E-cadherin. Cancer Res. 2000; 60: 298-304.
21. Siitonen SM, Kononen JT, Helin HJ, et al. Reduced Ecadherin expression is associated with invasiveness and unfavorable prognosis in breast cancer. Am J Clin Pathol.1996; 105: 394-402.
22. De Leeuw WJ, Berx G, Vos CB, et al. Simultaneous loss of E-cadherinand catenins in invasive lobular breast cancer and lobular carcinoma in situ. J Pathol. 1997; 183: 404-411.
23. Gamallo C, Palacios J, Suarez A, et al. Correlation of E-cadherin expression with differentiation grade and histological type in breast carcinoma. Am J Pathol. 1993; 142: 987-993.

24. Moll R, Mitze M, Frixen UH, et al. Differential loss of E-cadherin expression in infiltrating ductal and lobular breast carcinomas. Am J Pathol. 1993; 143: 1731-1742.
25. Goldstein NS. Does the level of E-cadherin expression correlate with the primary breast carcinoma infiltration pattern and type of systemic metastasis? Am J Clin Pathol. 2002; 118: 425-434.
26. Lipponen P, Saarelainen E, Ji H, et al. Expression of E-cadherin as related to other prognostic factors and survival in breast cancer. J Pathol. 1994;174: 101–109.
27. Rimm DL, Sinard JH, Morrow JS. Reduced alpha-catenin and E-cadherin expression in breast cancer. Lab Invest. 1995; 72 (5): 506–512.
28. Parker C, Rampaul RS, Pinder SE, et al. E-cadherin as a prognostic indicator in primary breast cancer. Br J Cancer. 2001; 85 (12): 1958–1963.
29. Rubin MA, Mucci NR, Figurski J, et al. E-cadherin expression in prostate cancer: a broad survey using high-density tissue microarray technology. Hum Pathol. 2001; 32: 690-697.
30. Suciu C, Cîmpean AM, Mureşan AM, et al. E-cadherin expression in invasive breast cancer. Rom J Morphol Embryol. 2008; 49 (4): 517–523.
31. Nikiel B, Chekan M, Jaworska M, et al. Expression of the selected adhesive molecules (cadherin E, CD44,LGAL3 and CA50) in papillary thyroid carcinoma. Pol J Endocrinol. 2006; 57 (4): 32-37.
32. Qureshi H, Linden M, Divine G, et al. 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): 377-85.
33. Makdissi F, Machado L, Oliveira A. Expression of E-cadherin, Snail and Hakai in epithelial cells isolated from the primary tumor and from peritumoral tissue of invasive ductal breast carcinomas. Braz J Med Biol Res. 2009; 42 (12): 1128-1137.
34. Rakha EA, Abd El Rehim D, Pinder SE. E-cadherin expression in invasive non-lobular carcinoma of the breast and its prognostic significance. Histopathology 2005; 46 (6): 685-93.
35. Guriec N, Marcellin L, Gairard B, et al. E-cadherin mRNA expression in breast carcinomas correlates with overall and disease-free survival. Invasion Metastasis 1996; 16: 19-26.
36. Berezhnaya N, Belova O, Vinnichuk Y, et al. Expression of e-cadherin in drug resistant human breast cancer cells and their sensitivity to lymphokine-activated lymphocytes action Exp Oncol. 2009; 31 (4): 242–245.
37. Heimann R, Lan F, McBride R, Hellman S. Separating favorable from unfavorable prognostic markers in breast cancer: the role of E-cadherin. Cancer Res. 2000; 60 (2): 298–304.
38. Bukholm IR, Nesland JM, Bukholm G. Expression of adhesion proteins E-cadherin, alpha-catenin, beta-catenin and gamma-catenin is different in T1 and T2 breast tumours. Pathology 2006; 38 (5): 403-7.
39. Da Silva BB, dos Santos Ar, Pires CG. E-cadherin expression in estrogen receptor-positive and negative breast carcinomas of postmenopausal women. Eur J Gynaecol Oncol. 2010; 31 (1): 90-3.
40. Mohammadizadeh F, Ghasemibasir H, Rajabi P. Correlation of E-cadherin expression and routine immunohistochemistry panel in breast invasive ductal carcinoma. Cancer Biomark. 2009; 5 (1): 1-8.