ORIGINAL ARTICLE

CONTENTS

Evaluation of E-cadherin expression in invasive ductal breast cancer

Ilona V. Chelpanova[1], Liliya I. Volos[1], Andrii P. Dudash[2], Yevgen V. Paltov[1], Artur V. Poliiants[3], Olha V. Dudok[1], Yulia V. Hnidyk[1]

[1]STATE NON-PROFIT ENTERPRISE «DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY», LVIV, UKRAINE
[2]WESTERN UKRAINIAN HISTOLOGICAL LABORATORY, LVIV, UKRAINE
[3] INTERNATIONAL MEDICAL CENTER LLC, KYIV, UKRAINE

ABSTRACT

Aim: To evaluate E-cadherin expression in various clinical and pathological prognostic scenarios to determine its significance in the development of molecular subtypes of invasive ductal breast cancer.

Materials and Methods: A comprehensive morphological and immunohistochemical study of 80 cases of invasive ductal carcinoma (IDC) was conducted to determine the molecular phenotype. The expression of E-cadherin, ER, PR receptors, c-erbB2, and Ki-67 was evaluated according to the manufacturer's standardized protocols using appropriate positive and negative controls. The degree of tumor malignancy was determined using the modified Scarff-Bloom-Richardson system. Semi-quantitative assessment of E-cadherin expression was performed using the Qureshi scale. Pearson's criterion was used for statistical analysis. Differences were considered statistically significant at $p < 0.05$.

Results: Low E-cadherin expression was associated with stage 3, pT3, and G2/G3 grades of IDBC malignancy, confirming its unfavorable prognostic significance and correlation with the molecular profile. High E-cadherin expression was characteristic of ER-positive luminal A tumors, regardless of menopause, indicating a regulatory role for ER expression. The low proliferative activity of luminal IDBC cells was explained by high E-cadherin expression, which increased adhesive properties. Low E-cadherin expression is also a prognostic marker for TNBC.

Conclusions: E-cadherin is a potent tumor suppressor in breast cancer. Its role in disease progression is confirmed by the correlation between partial or complete loss of E-cadherin expression and poor prognosis for patients.

KEY WORDS: E-cadherin expression, morphological and immunohistochemical study, invasive ductal breast cancer, molecular phenotype

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INTRODUCTION

Breast cancer (BC) is a significant global health problem, being the most commonly identified cancer among women and ranking second in terms of mortality from cancer. According to the World Health Organization strategy, the key objective in the fight against BC is to achieve an annual reduction in global mortality, potentially preventing millions of deaths worldwide by 2040.

The strategy, which aims to reduce global breast cancer mortality by 2.5% annually, envisages preventing 25% of deaths by 2030 and 40% by 2040 among women under the age of 70. Experts emphasize that achieving these goals requires strengthening health measures for early detection, rapid diagnosis, and a comprehensive approach to breast cancer treatment [1]. And also taking into account the current trends in modern reconstructive and cosmetic surgery, such as augmentation mammoplasty, which is not usually associated with an increased risk of cancer, although it has an aesthetic purpose, may contribute to the early detection and timely diagnosis of breast cancer [2]. The current understanding of (BC) defines it as a spectrum of diseases with diverse morphology, unique molecular profiles, clinical courses, and responses to treatment [3]. In the context of the development of personalized medicine based on individual patient characteristics, despite the expansion of therapeutic options, traditional clinical-pathological and already known molecular prognostic markers are insufficient to reflect this degree of heterogeneity. For a successful, so-called "targeted" approach to therapy and improved cancer treatment efficacy, both additional molecular markers and prognostic biomarkers are critically important.

Accurate prognostic stratification is critically important because it allows patients with a good prognosis, who can avoid potentially toxic systemic therapy, to be distinguished from patients with a poor prognosis who require more intensive forms of treatment. It is for this second group that the use of prognostic markers allows the most appropriate therapy to be determined, which will increase the chances of success and reduce the risk of side effects. Although HER2/neu and hormone receptors are the main prognostic factors in the routine diagnosis of breast cancer for targeting targeted therapy and provide some prognostic information, they do not solve all problems. Luminal tumors (ER-positive, HER2/neu-negative) account for a significant proportion of BC cases—almost 60% in the early stages with negative lymph nodes and over 50% of all molecular subtypes [4]. HER2/neu-positive (12-20%) and triple-negative (15-20%) BC are recognized as aggressive tumors associated with poor outcomes; unfavorable prognostic parameters of the disease are also found in younger patients [5]. In addition to breast cancer subtypes, histological assessment provides significant prognostic information, according to the 2013 St Gallen consensus [6].

Given the rising costs of healthcare and the emergence of new targeted therapies, the use of biomarkers has become an integral part of breast cancer diagnosis, predicting treatment response, and monitoring disease progression during and after treatment.

Over the past decade, numerous research centers have been actively investigating new prognostic factors based on molecular characteristics of tumors in patients with BC. In modern oncology, the priority area of molecular genetic research is the identification of genomic abnormalities that affect tumor development, malignancy, metastatic potential, and progression rate.

As a result, molecular morphopathology becomes crucial for tumor prediction. It analyzes the presence or absence of oncogenes and tumor growth suppressors (molecular biological markers) in cells, since differences in the expression of these markers can explain the varying aggressiveness of tumors that are comparable in prevalence and histological structure [7]. Analysis of molecular biological markers in tumor tissue provides a deeper understanding of its biological characteristics, such as growth rate, invasive and metastatic potential, and chemoresistance.

E-cadherin (epithelial cadherin) is one of the key markers that functions as a potent suppressor of tumor invasion and metastasis, providing cell adhesion, and its selective loss in human carcinomas can lead to dedifferentiation and increased invasiveness, confirming its role as a tumor suppressor [8]. The main cell adhesion molecule in epithelial tissues, E-cadherin, is encoded by the CDH1 gene located on chromosome 16q22.1 [9, 10]. This polypeptide, consisting of 728 amino acid residues, is expressed on the surface of epithelial cells. Among the most important features of the multistage process of metastasis is the deformation of adhesive contacts of neoplastic cells, which is caused by a violation of cadherin expression [11]. In addition, epithelial-mesenchymal transformation also plays a critical role in this process. Although epithelial-mesenchymal transformation (EMT) is similar to the processes of embryonic development, its decisive difference lies in its uncontrolled nature [12]. It is this transformation in epithelial tumors that provides their ability to invade and metastasize [13]. The significant role of E-cadherin as a tumor suppressor encoded by the CDH1 gene [14] is emphasized by the fact that its loss or abnormal expression promotes the invasion of neoplastic cells. In cases of breast cancer, a decrease in E-cadherin levels is observed in approximately 50% of invasive ductal carcinomas and reaches 90% in invasive lobular carcinoma, predominantly among tumors with a triple-negative phenotype [12]. A number of authors also point to a correlation between aberrant E-cadherin expression and disease stage, metastatic potential, and frequent absence of ER expression [15].

Morphological studies of breast cancer, especially with the introduction of immunohistochemical (IHC) methods, have become crucial, as their results allow not only to predict the course of the disease, but also to determine the direction of antitumor therapy [16]. Thus, preliminary data indicate the important role of E-cadherin protein expression.

It has been established that reduced expression of E-cadherin during tumor development triggers a cascade of signaling mechanisms, providing tumor cells with a more invasive phenotype, increasing their ability to migrate and survive, and promoting the development of distant metastases.

Research into the correlation between E-cadherin expression, lymph node metastasis status, clinical and pathological parameters, and the molecular phenotype of invasive ductal breast cancer is becoming increasingly important. The assessment of E-cadherin expression is recognized as a key prognostic marker for the course of breast cancer. Therefore, any deviations associated with abnormal expression or dysfunction of these cell adhesion molecules can have profound destructive consequences.

AIM

This study aim was to evaluate E-cadherin expression in various clinical and pathological prognostic scenarios

Table 1. Antibody panel for IHC testing

Antibody	Clone	Immunized animal	Manufacturer	Localization in the cell
E-cadherin	Clone HECD-1	monoclonal mouse antibodies	Master diagnostica	Membrane
ER	Clone SP1	monoclonal rabbit antibodies	Dako	Nucleus
PR	PgR 636	monoclonal mouse antibodies	Dako Flex	Nucleus
c-erbB2	Clone SP3	monoclonal rabbit antibodies, to Her2/neu	Thermo scientific	Membrane
Ki-67	Clone MIB-1	monoclonal mouse antibodies	Dako	Nucleus

Source: compiled by the authors of this study

to determine its significance in the development of molecular subtypes of invasive ductal breast cancer.

MATERIALS AND METHODS

The study covered 80 cases of invasive ductal breast cancer using immunohistochemical examination and analysis of E-cadherin expression. Immunohistochemical analysis of E-cadherin revealed immunoreactivity of varying degrees of intensity depending on the age of the patients, disease stage, tumor size, G malignancy grade, lymph node involvement, and different molecular subtypes of breast cancer.

In all cases, the diagnosis of the breast invasive ductal carcinoma was verified histologically. The histological type of cancer was determined in accordance with WHO recommendations [17]. Tumor grading according to the degree of malignancy was performed based on modified criteria by P. Scarff, H. Bloom, and W. Richardson [18].

After studying the clinical and pathomorphological information and dividing the sample into molecular subtypes according to the 2015 St. Gallen consensus [19], the following observation groups were formed: luminal A subtype (21 cases); luminal B subtype (19); Her2/neu (20); triple-negative (20).

The Bioethics Committee of Danylo Halytsky Lviv National Medical University (protocol No. 3 dated March 11, 2020) has established that all animals were housed in a vivarium and procedures for cleaning, inspection, marking and all other manipulations were carried out in accordance with the provisions of the «European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes» (Strasbourg, 1986), the «General Ethical Principles of Experiments on Animals» adopted by the First National Congress on Bioethics (Kyiv, 2001), the Law of Ukraine No. 3447-IV «On the Protection of Animals from Cruel Treatment» in accordance with the Directive of the Council of the European Union 2010/63/EU on compliance with the regulations, laws, and administrative provisions of the EU Member States on the protection of animals used for scientific purposes [20,21].

Histological studies of surgical material were performed using a Leica DM750 universal light microscope (Leica Microsystems GmbH) by a standard method [22]. Immunohistochemical examination was performed on serial paraffin sections of tumor tissue (invasive ductal breast cancer) according to the manufacturer's protocols. After deparaffinization, rehydration, temperature unmasking of antigens, and suppression of endogenous peroxidase activity, the sections were incubated with monoclonal antibodies in humid chambers at 23-25°C for 30 minutesThe DAKO EnVision+System visualization system was used. To identify the reaction, a solution of chromogen 3-diaminobenzidine tetrachloride ("DAKO", USA) was applied under microscopic control for 20 seconds to 3 minutes, with a brown color appearing. Then, we additionally stained with Mayer's hematoxylin for 1-3 minutes, followed by dehydration and fixation with balsam according to the standard procedure [23,24].

The immunohistochemical status of E-cadherin, estrogen receptor (ER), progesterone receptor (PR), c-erbB2 oncoprotein, and Ki-67 proliferation index expression was studied using the manufacturer's protocols with the necessary controls. For samples with Her2/neu 2+ status, fluorescence in situ hybridization (FISH) was performed based on the results of immunohistochemical examination. The antibody data panel is presented in Table 1.

ASSESSMENT OF IMMUNOHISTOCHEMICAL STAINING

Positive ER and PR expression was established when ≥1% of neoplastic cells showed positive nuclear expression of any intensity [25]. ER and PR status were assessed according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines for ER and PR IHC testing. The threshold between low and high Ki-67 nuclear expression was set at ≥20% positive cells according to the 2015 St. Gallen Consensus. For Her2/neu IHC, only

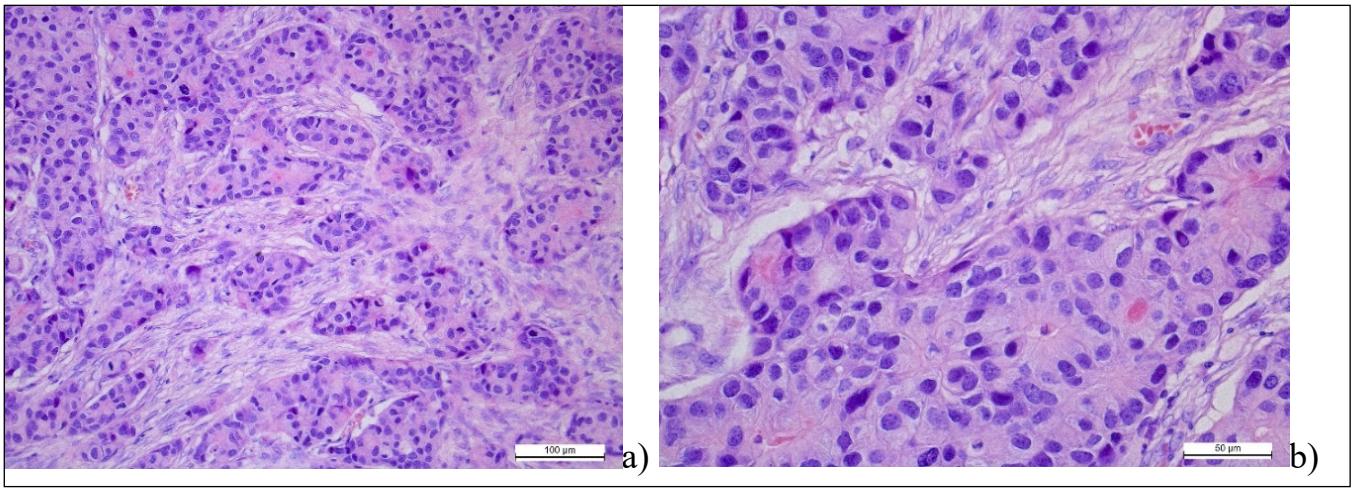

Fig. 1. Invasive ductal breast carcinoma: solid structures in the invasive component. Hematoxylin and eosin staining. a) ×200; b) ×400
Picture taken by the authors

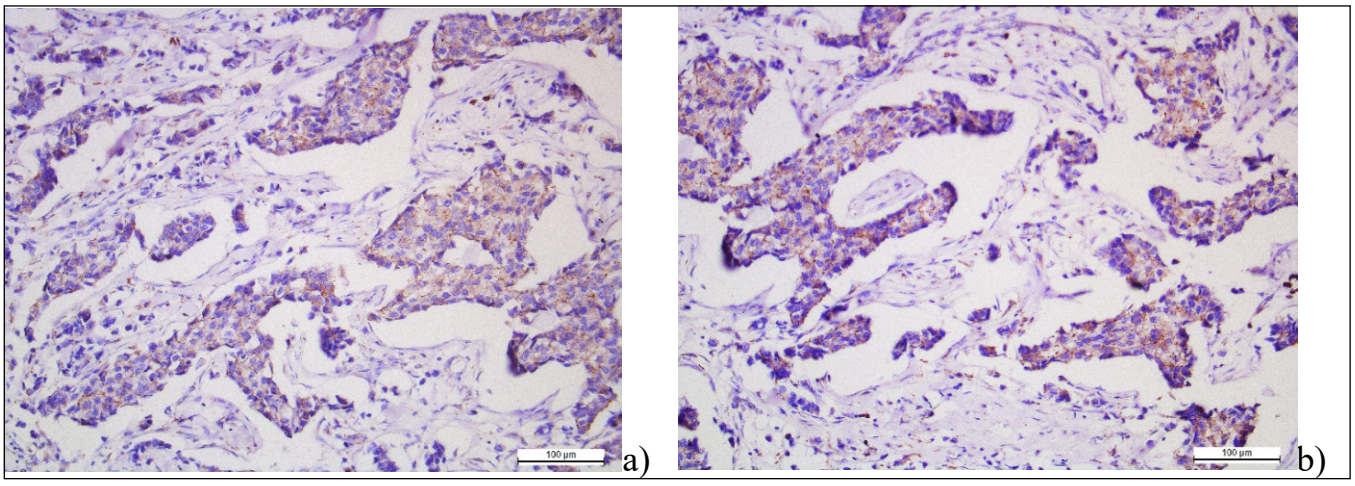

Fig. 2. Invasive ductal breast carcinoma : a) no immunoreactivity with antibodies to E-cadherin (×200); b) membrane positivity in <10% of tumor cells (0 points). ×200
Picture taken by the authors

membrane staining was considered, and more than 10% strong membrane positivity was accepted as positive (3+) Her2/neu according to CAP recommendations.

E-cadherin reaction was evaluated using a scoring system developed by Qureshi et al. [26], in which E-cadherin expression was assessed according to the percentage of positive cells and staining intensity in five fields of view at ×400 magnification. Scoring: 0 – no staining or membrane positivity in <10% of tumor cells; 1 – incomplete and weak membrane staining in >10% of tumor cells; 2 – complete membrane staining with weak or moderate intensity in >10% of tumor cells; 3 – strong membrane staining in >10% of tumor cells. According to this assessment, the reaction was considered negative for scores 0 and 1, weakly positive for scores 2, and strongly positive for scores 3. Cytoplasmic staining was considered nonspecific and was not included in the assessment. The presence of E-cadherin staining in epithelial cells of normal ducts and acini served as an internal positive control. All specimens were evaluated by two pathologists to ensure consistency.

STATISTICAL PROCESSING OF RESEARCH RESULTS

Statistical analysis of the results was performed using the R Commander program. The data are presented as percentages with 95% confidence intervals (% [95% CI]), calculated using Fisher's angular transformation criterion-φ. The comparison of the degree of E-cadherin expression at different clinical and pathological parameters and different molecular phenotypes was evaluated using Pearson's criterion. For all types of analysis, differences were considered significant at $p<0.05$.

RESULTS

Epithelial cadherin (E-cadherin) is an important member of the cadherin family, playing a major role

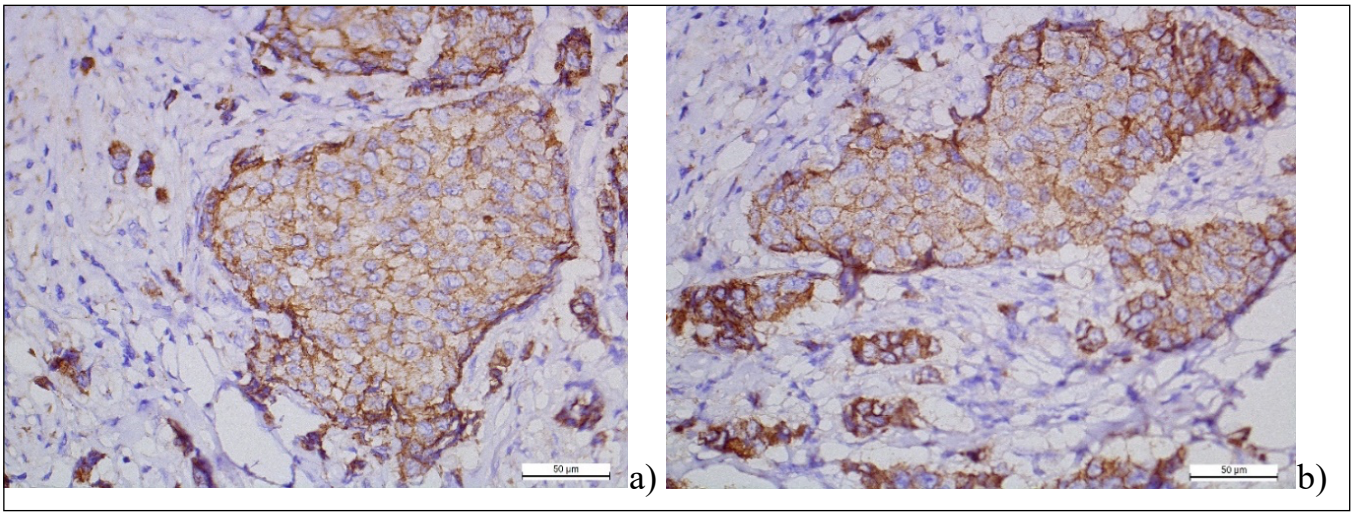

Fig. 3. Invasive ductal breast carcinoma , E-cadherin expression: incomplete (a) and weak (b) membrane staining >10% of tumor cells (1 point). ×400
Picture taken by the authors

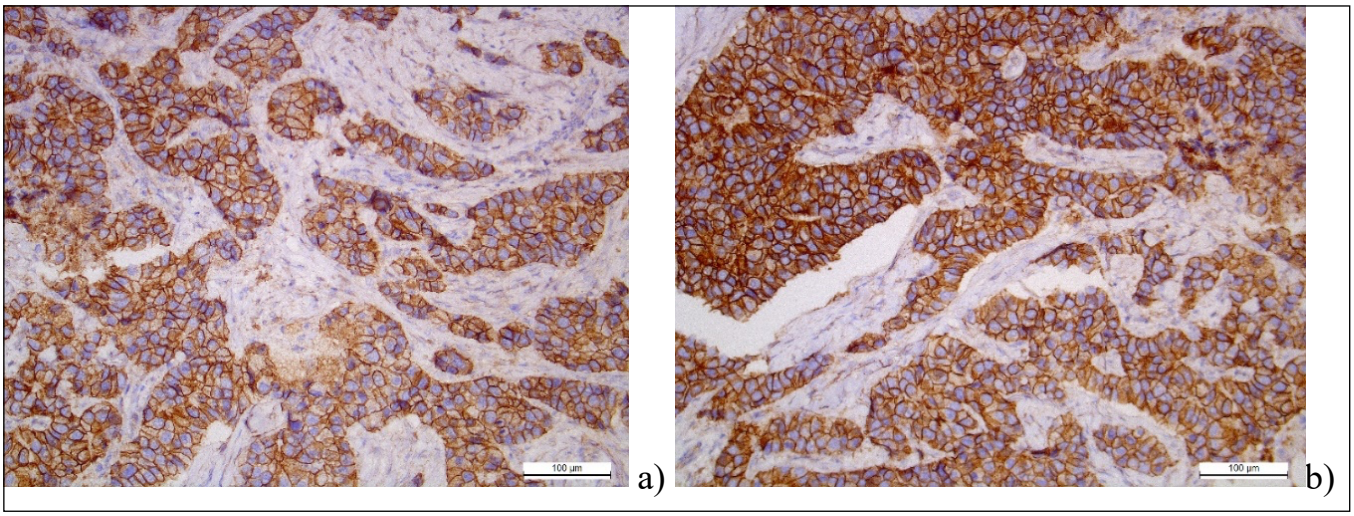

Fig. 4. Invasive ductal breast carcinoma, E-cadherin expression: complete membrane staining with weak (a) or moderate (b) intensity in >10% of tumor cells (2 points). ×200.
Picture taken by the authors

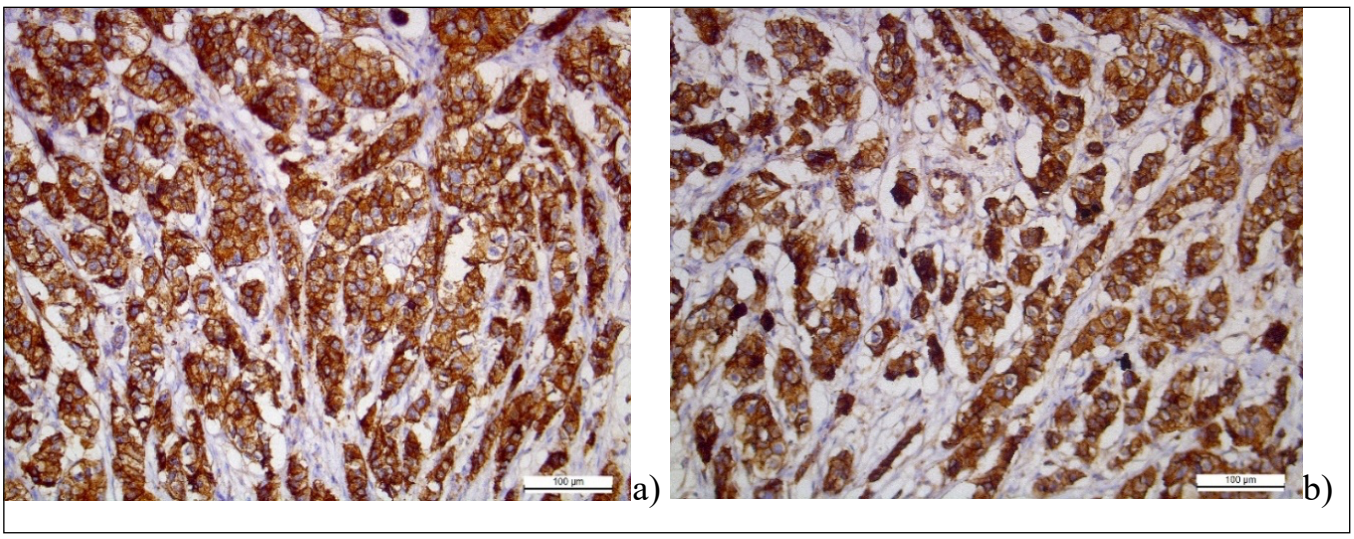

Fig. 5. Invasive ductal breast carcinoma, E-cadherin expression: strong membrane staining in >10% of tumor cells (3 points). ×200
Picture taken by the authors

in cell adhesion and acting as a powerful suppressor of invasion and metastasis. One of the most important features of the metastasis process is the deformation of adhesive contacts of neoplastic cells, mediated by impaired expression of cadherins. Another important feature of the metastasis process is the implementation of epithelial-mesenchymal transformation, which ensures the tumor's ability to invade and metastasize. Selective loss of E-cadherin can cause dedifferentiation and invasiveness in human carcinomas, so this marker is considered a tumor suppressor.

Prior to IHC analysis, the specimens were examined using routine hematoxylin and eosin staining (Fig. 1). E-cadherin was expressed as membrane staining. E-cadherin expression was graded as "0" – absence (Fig. 2a), membrane positivity in <10% of tumor cells (Fig. 2b), "1" – incomplete and weak membrane staining (Fig. 3a,b), "2" – complete membrane staining with weak or moderate intensity (Fig. 4a,b) and "3" – strong membrane staining in >10% of tumor cells (Fig. 5) based on the intensity of epithelial cell membrane staining.

Comparison of E-cadherin expression and lymph node metastasis showed that positive E-cadherin expression varied in intensity and included both low and high expression.

High expression levels were found in cases of non-metastatic tumors and tumors with micrometastases in the lymph nodes ($p<0.05$). It was found that E-cadherin expression in ductal breast cancer tissue was significantly lower in the presence of lymph node metastases than in the absence of metastatic lymph node involvement ($p<0.05$), i.e., low E-cadherin expression was associated with metastases in lymph nodes.

E-cadherin expression showed insignificant differences in terms of patient age, i.e., whether patients were in menopause or premenopause. Thus, in patients under 50 years of age, negative and low E-cadherin expression was found in 54% of cases, while high expression of 3 points was diagnosed in 46% of patients, $p>0.05$. Patients over 50 years of age were characterized by both high positive expression of E-cadherin and low and negative expression, but there was no significant difference in the age of patients, $p>0.05$.

E-cadherin expression showed significant differences in disease stages according to TNM classification. In stage T1 and tumor size less than 2 cm, high E-cadherin expression was diagnosed in 68% of cases ($p<0.005$). In stage T3 breast cancer and with a tumor size greater than 5 cm, negative and low expression was diagnosed in 78% of cases ($p<0.05$), i.e., patients with stage T1 were significantly associated with positive E-cadherin expression, while patients with stage T3 were significantly associated with low and negative E-cadherin expression.

A similar pattern was observed in the study of E-cadherin expression in patients with clinical stage 1 with a tumor size of up to 2 cm in the largest diameter without metastatic lymph node involvement and clinical stage 3 with a tumor size of more than 5 cm in the largest diameter, with metastases in regional and distant lymph nodes, in moderately differentiated and poorly differentiated tumors, respectively, $p<0.05$ and $p<0.001$.

Significant results were observed between E-cadherin expression and G differentiation grade, $p<0.05$. In patients with moderately differentiated G2 and poorly differentiated G3 tumors, negative and low E-cadherin expression significantly prevailed over cases with high expression levels. Thus, low cell adhesion indices were determined in 65% of patients with G2 tumors, and high positive E-cadherin expression was found in 35% of patients, i.e., G2 tumors were significantly characterized by a predominance of negative and low E-cadherin expression, $p<0.01$. G3 tumors similarly manifested negative and low expression in 77%, which was more than 3 times higher than low-differentiated tumors with a high degree of E-cadherin expression (23%), $p<0.01$.

The association of E-cadherin expression with tumor receptor status and molecular-genetic phenotype of carcinomas was studied. Distribution of patients by receptor status: luminal A phenotype (21), luminal B phenotype (19), triple-negative breast cancer (20), Her2/neu-positive phenotype (20).

High expression of E-cadherin was common in ER-positive tumors, particularly in 64% of patients with luminal A phenotype carcinoma. It should be noted that high E-cadherin expression was determined in both premenopausal and postmenopausal patients, but patients over 50 years of age were significantly associated with positive E-cadherin expression.

In patients with luminal B breast cancer, E-cadherin testing showed low and negative expression in 55% and high levels in 45%. In age groups up to 50 years and over 50, low and negative expression slightly prevailed ($p>0.05$). A similar pattern was observed in the group of patients with Her2/neu-positive phenotype. Thus, 58% of patients showed negative and low expression, while 42% showed positive high expression. Low and negative expression also prevailed regardless of whether patients were in menopause or premenopause, and there were no significant differences with the subgroup in which positive high expression was observed ($p>0.05$).

With regard to triple-negative breast cancer, it should be noted that a significant predominance of patients with low and negative E-cadherin expression was found ($p<0.01$). In 70% of cases, low cell adhesion rates were observed, although most patients were over 50 years of age ($p<0.05$). In 30% of patients, high E-cadherin

expression was observed, mainly in the age group also over 50 years ($p<0.05$).

DISCUSSION

The incidence of breast cancer continues to rise, and it is currently the most common form of malignant tumor among women worldwide [27, 28]. The spread of breast cancer metastases affects the prognosis of the disease and is the main cause of mortality [29]. Breast cancer recurrence and metastasis are serious clinical problems.

Changes in cell adhesion are the main mechanism of malignant tumor invasion and metastasis. Changes in adhesion molecules can reduce tumor cell adhesion, promoting tumor infiltration and metastasis. Thus, decreased cell adhesion is an important factor leading to tumor metastasis [30]. Epithelial cadherin (E-cadherin) is a member of the cadherin family and plays an important role in the process of cell adhesion. Selective loss of E-cadherin can cause dedifferentiation and invasiveness in human carcinomas, leading to this marker being classified as a tumor suppressor. Consistent with this role in breast cancer progression, partial or complete loss of E-cadherin expression has been found to correlate with poor prognosis in patients [30- 33].

To determine the nature of E-cadherin protein expression and its possible clinical significance, 80 cases of invasive ductal carcinoma of the breast were studied. E-cadherin expression was detected using immunohistochemistry, and clinical and pathological features and molecular subtypes of invasive ductal carcinoma of the breast were compared according to E-cadherin expression levels. Research have shown that E-cadherin is closely associated with the infiltration and metastasis of ductal carcinoma of the breast and can be used as a marker for predicting metastasis to lymph nodes. High expression of E-cadherin has been detected in invasive tumor cells without metastasis. The negative expression rate was significantly higher in patients with breast cancer with local metastases to regional lymph nodes than in patients without lymph node metastases, and the differences were statistically significant ($p<0.05$).

Paredes J, Figueiredo et al. showed in their studies that, when epithelial-mesenchymal transformation occurs in cancer cells, E-cadherin expression decreases or demonstrates functional loss, causing decreased cell adhesion, loss of polarity, and infiltration of surrounding tissue [34]. E-cadherin has become one of the focal points of research among all cadherins, and it has been shown that E-cadherin is involved in the early onset, infiltration, and metastasis of various tumors [35, 36].

Loss of E-cadherin expression has an unfavorable prognostic significance. Its absence is often associated with metastatic lymph node status, tumor recurrence, low differentiation, and advanced tumor stage [37]. The results of this study showed significant differences in E-cadherin expression in stages T1 and T3 according to the TNM classification, i.e., when the tumor size was less than 2 cm and when it was greater than 5 cm. Positive E-cadherin expression was diagnosed in patients with stage T1 ($p<0.005$), while low and negative E-cadherin expression was observed in patients with stage T3 disease ($p<0.05$).

A similar pattern was observed in the study of E-cadherin expression in patients with clinical stage 1 with a tumor size of up to 2 cm in the largest diameter without metastatic lymph node involvement and clinical stage 3 with a tumor size of more than 5 cm in the largest diameter, with metastases in regional and distant lymph nodes, in moderately differentiated and poorly differentiated tumors, respectively, $p<0.05$ and $p<0.001$.

Significant results were observed between E-cadherin expression and G differentiation grade, $p<0.05$. In patients with moderately differentiated G2 and poorly differentiated G3 tumors, negative and low E-cadherin expression prevailed several times over cases with high expression. Positive immune response decreased with tumor dedifferentiation. In poorly differentiated tumors, E-cadherin expression was weak, with membrane positivity in less than 10% of tumor cells, equal to 0 points or absent (Fig. 2). Not all cells were stained, and positive cells showed abnormal staining patterns, with only focal and punctate membrane positivity, which was equal to 1 point (Fig. 3). In moderately differentiated tumors, E-cadherin expression was heterogeneous: complete membrane staining with weak or moderate intensity in more than 10% of tumor cells and equal to 2 points (Fig. 4). In contrast, high E-cadherin expression prevailed in patients with highly differentiated carcinomas, with strong membrane staining in more than 10% of tumor cells, equal to 3 points (Fig. 5).

The results of this study demonstrated that E-cadherin expression was associated with the molecular type of invasive ductal carcinoma of the breast. In the luminal A phenotype, E-cadherin expression was high in 64% of patients, predominantly in those over 50 years of age, indicating that ER-positive expression may be involved in the regulation of E-cadherin expression. The literature also shows that low tumor activity of invasive ductal breast cancer cells of the luminal subtype is accompanied by an increase in the adhesive properties of these cells due to high levels of E-cadherin expression [38].

Today, according to researchers, E-cadherin is considered an independent marker of triple-negative breast cancer, a molecular subtype characterized by

poor prognosis and short life expectancy [39]. This study found a significant predominance of patients with low and negative E-cadherin expression ($p<0.01$). Low cell adhesion rates were observed in 70% of cases, although most patients were over 50 years of age ($p<0.05$). In the triple-negative phenotype, E-cadherin showed low expression, which was closely associated with invasion and metastasis.

E-cadherin expression in HER-2-positive and luminal B phenotypes was low in most observations and even negative in both premenopausal and postmenopausal patients, In contrast, high expression was determined in 45% of observations of the luminal B phenotype and in 42% of Her2/neu-positive cases. In addition, low and negative expression prevailed regardless of whether patients were menopausal or premenopausal, and there were no significant differences with the subgroup in which positive high expression was observed ($p>0.05$). The different oncogenicity of HER-2-positive and luminal B phenotypes is associated with changes in adhesive contacts, which is due to disturbances in E-cadherin expression.

CONCLUSIONS

The results of the study and data from the literature allowed us to analyze the immunoreactivity of E-cadherin depending on the age of patients, stage of disease, tumor size, degree of malignancy G, involvement of lymph nodes in the tumor process, as well as in different molecular subtypes of breast cancer.

It has been established that low expression of E-cadherin or its absence was associated with moderately differentiated and poorly differentiated tumors of stage T3, clinical stage 3, and the presence of metastases in the lymph nodes. Loss of E-cadherin expression has an unfavorable prognostic significance.

E-cadherin expression was associated with the molecular type of invasive ductal carcinoma of the breast. High E-cadherin expression was common in ER-positive luminal A phenotype tumors and was detected in both premenopausal and postmenopausal patients, suggesting that ER-positive expression may be involved in the regulation of E-cadherin expression. Low tumor activity of invasive ductal breast cancer cells of the luminal subtype is accompanied by an increase in the adhesive properties of these cells due to high levels of E-cadherin expression.

E-cadherin is considered an independent marker of triple-negative breast cancer and is characterized by an unfavorable prognosis and short life expectancy for patients. Triple-negative cancer was associated with a significant predominance of patients with low and negative E-cadherin expression ($p<0.01$).

Thus, E-cadherin is a potent tumor suppressor in breast cancer. Consistent with this role in breast cancer progression, partial or complete loss of E-cadherin expression has been found to correlate with poor prognosis in patients.

Prospects for further research are related to determining whether there are differences in E-cadherin expression in primary breast cancer cells and their metastases. Assessment of the E-cadherin tumor marker, which is involved in cell adhesion, may be a useful method for assessing the risk of metastasis in patients with breast cancer.

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A complete list of references is available upon request from the author.

CONFLICT OF INTEREST

The Author declares no conflict of interest

CORRESPONDING AUTHOR
Ilona V. Chelpanova
Danylo Halytsky Lviv National Medical University
52. Pekarska St, 79010 Lviv, Ukraine
e-mail: ilona.med75@gmail.com

ORCID AND CONTRIBUTIONSHIP
Ilona V. Chelpanova: 0000-0001-5215-814X B C D
Liliya I. Volos: 0000-0002-1733-589X A E F
Andrii P. Dudash: 0000-0002-7934-8995 B C D
Yevgen V. Paltov: 0000-0003-2611-0294 B E
Artur V. Poliiants: 0000-0002-2622-4753 B C F
Olha V. Dudok: 0000-0001-9513-3460 C E
Yulia V. Hnidyk: 0000-0002-6830-7143 C E

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