Original Article

E-cadherin Expression in Invasive Mammary Carcinoma

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Abstract

Background: E-cadherin is an adhesion molecule that is frequently expressed in normal epithelial tissues. It is essential for many cellular processes, including organ formation, stratification, and epithelial polarization. **Objective:** This study examines E-cadherin expression for subclassifying invasive breast cancer. E-cadherin expression also decreased with age, histopathological type, grade, and stage. **Materials and Methods:** This prospective study included 249 breast cancer patients who underwent surgery at a private facility in Baghdad, Iraq. The patients' clinical data were analyzed, focusing on age, histopathological type, tumor grade, and tumor stage. Immunohistochemical and histopathological processing and staining were performed to evaluate E-cadherin status in the tumor cells. **Results:** Mean age of patients 47.92 ± 10.79 years, most age group 40–49 (35.7%), most histopathological type of breast cancer invasive ductal carcinoma (IDC; 81.1%), grade II (67.9%), and stage II (78.3%). Patients have +3 E-cadherin (79.5%). Grade III breast cancer patients have 98% +3 E-cadherin. E-cadherin is unrelated to age, histopathological type, or stage. **Conclusion:** Decreased E-cadherin expression in breast cancer is associated with higher tumor grade and estrogen receptor status. However, its significance as a prognostic or predictive marker is limited in IDC and special varieties. The study found no significant correlation between E-cadherin expression and age group, histopathological type, or breast cancer stage.

Keywords: Carcinoma, E-cadherin, expression, invasive, mammary

Introduction

In healthy epithelial tissues, the adhesion molecule E-cadherin is frequently expressed.[1] It is crucial for a variety of cellular functions, such as stratification, epithelial polarization, and organ development.[2,3] The E-cadherin gene is found on chromosome 3's 16q22.1 region. Because E-cadherin-deficient animals generate abnormal epithelia and die, studies using knockout mice have shown that E-cadherin is necessary for proper epithelial morphogenesis.[4] Human carcinomas' dedifferentiation and invasiveness have both been associated with loss of E-cadherin expression.[4] In multiple cell lines, studies[5] have shown a connection between E-cadherin expression and invasiveness. In addition, aggressive esophageal, ovarian, and stomach tumors have been found to express E-cadherin less than normal.[6] The decrease in E-cadherin expression in cancer may be ascribed to many mechanisms, such as mutations occurring in the E-cadherin gene and the loss of the normal allele owing to loss of heterozygosity.[7,8] Based on the results of this study, it can be concluded that E-cadherin has characteristics consistent with those of a conventional tumor suppressor gene.[9] With ductal and lobular carcinomas being the most common types, infiltrating carcinomas make up the majority of breast cancers. On a histopathologic level, mammary carcinomas are typically classified as either invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC). However, this categorization may be challenging owing to overlapping histopathologic characteristics, notably with certain forms of ILC and pleomorphic ILC.[10,11] Significant prognostic ramifications result from accurate histopathologic classification of breast carcinomas.[12] It was discovered that E-cadherin expression was completely absent in a significant portion of ILCs.[13,14] E-cadherin expression is lost even in the preinvasive stage of lobular carcinoma *in situ* (LCIS), which explains why LCIS has distinct histopathologic features like a diffuse growth pattern and discohesive

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tumor cells.[15] E-cadherin expression has the potential to be a valuable diagnostic and prognostic biomarker in breast cancer, although its application is still debatable. Reduced E-cadherin expression has been linked to a poor prognosis in numerous studies.[16,17] Only a small number of studies, however, found links between nodal metastasis[18] and reduction of estrogen receptor (ER) and progesterone receptor expression.[19] In addition, studies have shown different relationships between E-cadherin expression and a variety of prognostic indicators and survival outcomes,[20] disregarding histopathologic grade. This study aims to evaluate E-cadherin expression as a strategy for invasive breast cancer subclassification. Additionally, there was a correlation between the loss of E-cadherin expression and age (years), histopathological type, grade, and stage.

Materials and Methods

Cases/study group: It is prospective research in which breast cancer specimens were obtained from women undergoing surgery at a private facility in Baghdad, Iraq, after a radical modified mastectomy. Between March 2021 and February 2023, a total of 249 patients diagnosed with breast cancer histopathologically were included and studied. Formalin-fixed, paraffin-embedded tissue was used to represent these specimens, which included 202 cases of IDC, 40 cases of ILC, and 7 cases of invasive mixed (ductal and lobular) mammary carcinoma/high-grade. Patient's clinical data were analyzed with a focus on age, histopathological type, tumor grade, and tumor stage. The immunohistochemical and histopathological processing and staining: The blocks are sectioned to a thickness of 4 µm, stained with Hematoxylin and Eosin, and submitted for histopathological analysis. According to the WHO classification fifth edition, 2019, the histopathological classification used to determine the form of breast cancer has been completed.[20] According to a modified Bloom-Richardson grading system, the level of differentiation (grading system) was evaluated. According to American Joint Committee on Cancer Staging, 2021, eighth edition (AJCC Cancer Staging, 2021),[21] the tumor's stage was determined. Concerning immunohistochemically marker (E-cadherin), representative paraffin-embedded blokes containing breast cancer tissue from all cases were used to obtain sections of 4 µm thickness placed on positively charged slides used to evaluate the E-cadherin status (Monoclonal antibody "M3612", Dako), utilizing the avidin–biotin complex detection system. Using a scoring system (membrane staining),[22] the E-cadherin reaction in tumor cells was measured. Cytoplasmic staining was deemed nonspecific and was excluded from the evaluation. E-cadherin was scored using a four-point system as follows: weak = 1+, intermediate = 2+, and strong = 3+. Scores for staining intensity ranged from 0 to 3, with 0 representing total absence or negativity, 1 representing a bright membrane expression of less than 10%, 2 representing a bright membrane expression of more than 10% but less than 50%, and 3 representing a bright membrane expression of more than 50%. Using SPSS 22, the statistical analysis was carried out. Frequency and percentage metrics were used to examine categorical data, whereas mean, median, and standard deviation were used to evaluate continuous data. A common method for analyzing the correlation between categorical data is the chi-square test. Statistical significance is defined as a $P \leq 0.05$.

Ethical approval

The study was conducted in accordance with the ethical guidelines established by the Helsinki Declaration. Before a sample was taken, it was carried out with the patients' verbal and analytical consent. A local ethics committee reviewed and approved the study protocol and the subject information and consent form in accordance with document number 186 (including the number and the date in Mach 1, 2021) to acquire this permission.

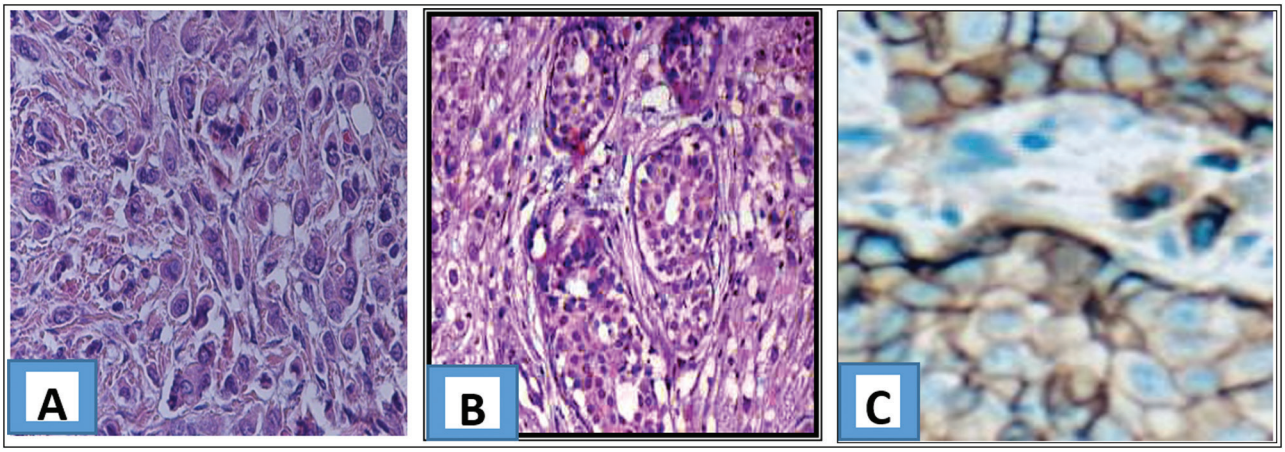

Figure 1: (A) Invasive ductal carcinoma, stained with H & E, magnification = 400×. (B) Invasive lobular carcinoma, stained with H & E, magnification = 400×. (C) E-cadherin strong positive immunoreactivity in invasive ductal carcinoma, magnification = 400×

Results

The mean age of patients was 47.92 ± 10.79 years old, most age groups 40–49 (35.7%), and the most histopathological type of breast cancer is IDC (81.1%), 67.9% of patients with breast Ca. at grade II and 78.3% of them at stage II [Figure 1]. About 79.5% of patients are at +3 E-cadherin as shown in Table 1.

As shown in Table 2; there is a significant association between E-cadherin and grade, 98% of females in grade III breast cancer have +3 E-cadherin. No significant association between age group and E-cadherin (years), histopathological type, and stage.

Discussion

Cell adhesion molecule E-cadherin is frequently found in healthy breast tissue and serves as an effective phenotypic marker in breast cancer. It typically does not exist in lobular tumors and is linked to negative outcomes such as decreased time without illness and worse overall survival rates. Additional bad prognostic indications include increased tumor size, greater histological grade, the prevalence of distant metastases, and the existence of ER-negative tumors, which are associated with decreased or impaired E-cadherin expression.[21] The study's breast cancer patients ranged in age from 47.92 to 10.79 on average, which shows a large age range. About 35.7% of all breast cancer patients were between the ages of 40 and 49. This data supports the widespread perception that middle-aged women are more likely than younger women to get breast cancer. In terms of the histological categorization of breast cancer, IDC was assigned to 81.1% of patients. IDC is the most frequent type of breast cancer and is distinguished by the development of cancer cells in the milk ducts and their subsequent invasion of the neighboring breast tissue.[23] The research also disclosed details on the grade and stage of breast cancer in the patient group. Grade II breast cancer patients made up 67.9% of the population, showing a moderate degree of cancer cell differentiation. About 78.3% of patients had stage II cancer, which means the disease had spread from the original site but hadn't yet metastasized to distant organs or lymph nodes.[24] E-cadherin expression was assessed in the research, and the findings showed that 79.5% of the patients had an enhanced level (+3) of E-cadherin expression. E-cadherin is normally expressed in healthy breast tissue and is necessary for cell adhesion. However, less favorable outcomes and more aggressive types of breast cancer have been associated with diminished or absent E-cadherin expression. Therefore, the majority of the patients in this research had higher E-cadherin expression, which may be a sign of a good prognosis.[25] According to the study, there is a strong link between the expression of E-cadherin and the stage of breast cancer. In particular, it was shown that E-cadherin expression (+3) was highly expressed in 98% of women with grade III breast cancer. This result suggests that the expression of E-cadherin and the grade of the malignancy are significantly correlated. Breast cancer patients have a worse prognosis and more aggressive tumor behavior when E-cadherin expression is low or absent.[26,27] The statistical significance of the association between the expression of E-cadherin and the grade of breast cancer was established. Particularly, 98% of patients with grade III breast cancer had strong E-cadherin expression (+3). This shows that when the grade of breast cancer grows, higher E-cadherin expression is more likely to occur. In several cancer types, including breast cancer, loss or decrease in E-cadherin expression has been associated with more aggressive tumor behavior and a higher tumor grade.[26,27] The decrease in E-cadherin expression was shown to be significantly correlated with cancer grade and ER status in the research. The study was performed without include ILCs, since prior research has shown that ILCs are frequently E-cadherin negative independent of their grade, nodal status, size, or hormonal state. A limited number of instances with IDC and certain variations showed a complete loss of E-cadherin, rendering it less useful as a prognostic or predictive marker in these specific cases.[21] E-cadherin expression, on the other hand, did not significantly correlate with age, histological type, or stage of breast cancer, according to the research. Although E-cadherin is known to contribute to the development

Table 1: Distribution of patients according to the variables of study

Variables	Frequency	Percentage
Age group (years)		
20–29	9	3.6
30–39	45	18.1
40–49	89	35.7
50–59	73	29.3
60	33	13.3
Histopathological type		
IC	7	2.8
IDC	202	81.1
ILC	40	16.1
Grade		
I	29	11.6
II	169	67.9
III	51	20.5
Stage		
I	3	1.2
II	195	78.3
III	42	16.9
IV	9	3.6
E-cadherin		
0	4	1.6
1+	1	0.4
2+	46	18.5
3+	198	79.5

Table 2: Association between E-cadherin and the variables of study

Variables	E-cadherin				Total	*P*-value
	0	1+	2+	3+		
Age group (years)						
20–29	0	0	2	7	9	0.215
	0.0%	0.0%	22.2%	77.8%	100.0%	
30–39	3	1	10	31	45	
	6.7%	2.2%	22.2%	68.9%	100.0%	
40–49	1	0	17	71	89	
	1.1%	0.0%	19.1%	79.8%	100.0%	
50–59	0	0	11	62	73	
	0.0%	0.0%	15.1%	84.9%	100.0%	
60	0	0	6	27	33	
	0.0%	0.0%	18.2%	81.8%	100.0%	
Histo types						
IC	0	0	2	5	7	0.95
	0.0%	0.0%	28.6%	71.4%	100.0%	
IDC	4	1	37	160	202	
	2.0%	0.5%	18.3%	79.2%	100.0%	
ILC	0	0	7	33	40	
	0.0%	0.0%	17.5%	82.5%	100.0%	
Grade						
I	3	0	9	17	29	**0.0001**
	10.3%	0.0%	31.0%	58.6%	100.0%	
II	1	1	36	131	169	
	0.6%	0.6%	21.3%	77.5%	100.0%	
III	0	0	1	50	51	
	0.0%	0.0%	2.0%	98.0%	100.0%	
Stage						
I	0	0	1	2	3	0.13
	0.0%	0.0%	33.3%	66.7%	100.0%	
II	4	1	44	146	195	
	2.1%	0.5%	22.6%	74.9%	100.0%	
III	0	0	1	41	42	
	0.0%	0.0%	2.4%	97.6%	100.0%	
IV	0	0	0	9	9	
	0.0%	0.0%	0.0%	100.0%	100.0%	

Bold values mean $P \leq 0.05$ (significant)

and spread of breast cancer, investigations on this topic have shown conflicting results.[28,29]

Conclusion

In this study, IDC was the dominant histopathological type. While most patients were diagnosed at grade II and stage II, a significant association was observed between high E-cadherin expression and grade III. No relationships were found between E-cadherin levels and age, histopathological type, or stage.

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Conflicts of interest

There are no conflicts of interest.

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