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Case Report

E- Cadherin

A study of E- Cadherin in Benign and Malignant Breast Lesions with its Correlation with Histopathology

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Introduction: Breast diseases are showing a rising trend worldwide. Several studies have been done to show the magnitude of the problem. Various breast lesions include inflammatory lesions, benign proliferative breast diseases like firoadenosis, fibrocystic disease papillomas etc. and various cancers. Much concern is given to malignant lesions of the breast. Breast cancer ranks first among malignant tumours affecting females in many parts of the world. **Study Design:** Cross-sectional study. **Sample Size:** The present study was conducted on 100 cases of breast tumors. The study was carried out to find out the histological type of lesion along with the role of E-cadherin in benign and malignant breast lesions. **Results:** Out of 100 cases studied, 22 cases were benign and 78 cases were malignant lesions. **Conclusion:** Present study demonstrates that E-cadherin is strongly expressed in all benign breast lesions and there is increasing loss of E-cadherin expression with increasing grade/severity of malignancy.

Keywords: E- Cadherin, Benign Breast Lesion, Malignant Breast Lesions, Histopathology

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Introduction

Breast diseases are showing a rising trend worldwide. Several studies have been done to show the magnitude of the problem [1]. Various breast lesions include inflammatory lesions, benign proliferative breast diseases like firoadenosis, fibrocystic disease papillomas etc. and various cancers [2]. Much concern is given to malignant lesions of the breast. Breast cancer ranks first among malignant tumors affecting females in many parts of the world [3]. The large majority of breast cancers are detected during the reproductive years. The incidence curve starts rising at puberty, increases steeply up to menopausal age, and levels off afterwards. However, breast cancer can develop at any age from childhood to old age [4]. The three most commonly diagnosed cancers among women in 2006 are the cancer of breast, lung and colon, accounting for 54% of estimated cancer cases in women [5]. Breast cancer alone is expected to account for 31% of all new cancer cases [6]. Breast carcinoma is the most common malignant tumour and the leading cause of carcinoma death in women, with more than 10,000,00 cases occurring worldwide annually [7]. With rising incidence and awareness, breast cancer is the commonest cancer in urban Indian females, and the second commonest in rural Indian women [8]. The present study has been conducted to evaluate the role of E-cadherin in the subclassification of breast carcinomas and to differentiate various types of breast carcinoma from benign lesions.

E-cadherin- E-cadherin is a member of a family of transmembrane glycoproteins responsible for the calcium-dependent cell-cell adhesion mechanism and has been demonstrated to be involved in organogenesis and morphogenesis [9-12]. E-cadherin is a calcium-regulated adhesion molecule expressed in most normal epithelial tissues. The E-cadherin gene is located on chromosome 16q22.1. E-cadherin is associated with gland formation, stratification, and epithelial polarization [13]. Selective loss of E-cadherin can cause dedifferentiation and invasiveness in human carcinomas [14]. Mechanisms by which E-cadherin protein expression is lost include E-cadherin gene mutation and loss of the wild-type allele by loss of heterozygosity, these data indicate that E-cadherin is a tumor suppressor gene [15]. E-cadherin exerts a potent invasion-suppressing role

In tumor cell lines and in vivo tumor model systems. Forced expression of E-cadherin decreased the proliferation of different mammary carcinoma cell lines. E-cadherin expression could be used as an aid for the subclassification of invasive breast cancers [16]. However, the practical applications of E-cadherin expression in breast cancer as a prognostic and diagnostic cancer biomarker remain controversial. Reduced E-cadherin expression was an adverse prognostic biomarker in some studies17. Although most studies show reduced expression of E-cadherin to be associated with high histopathologic grade and correlation with nodal metastasis [16].

Aims And Objectives

1. We aimed to study the correlation between histopathology and immunohistochemical analysis of E- cadherin in benign and malignant breast lesions.

2. To study the role of E- cadherin in differentiating benign versus malignant breast lesions.

Research Methodology

Study Design: Cross-sectional study.

Sample Size: The present study was conducted on 100 cases of breast tumors. The study was carried out to find out the histological type of lesion along with the role of E-cadherin in benign and malignant breast lesions.

Inclusion Criteria For Histopathological Examination-Resected breast tissue specimens suspected to have benign and neoplastic lesions along with all the mastectomy specimens.

Exclusion Criteria For Histopathological Examination

- Inadequate tissue sample.
- Autolysed tissue sample.

Study Tools: Pretested Semi-structured questionnaires were used.

Duration Of the Study: The duration of the study was 16 months.

Study Setting: The present study was a prospective study; cases were retrieved from the routine of histopathology service on the patients admitted in Nehru Chikitsalaya,

B. R. D. Medical College, Gorakhpur. The study was conducted in the Department of Pathology, B. R. D. Medical College, Gorakhpur UP.

Results

In the present study **(Table-1)** out of a total of 100 selected cases 22(22%) were benign and 78(78%) cases were malignant. In the present study **(Table-2)** out of 22 benign cases, the maximum number of cases were of fibroadenoma 14/22 (53.6%) followed by cases of fibrocystic disease 06/22 (27.3%) and 02/22(19.1%) cases of ductal hyperplasia**.**

Table 1: Distribution of cases according to their benign and malignant nature

Lesion	No. of cases	Percentage
Benign	22	22
Malignant	78	78

Out of 100 cases studied, 22 cases were benign and 78 cases were malignant lesions.

Table 2: Distribution of cases according to the histological classification of breast lesions

S. No	Histological Diagnosis	No. of cases	%
1.	Fibroadenoma	16	16
2.	Fibrocystic disease	04	04
3.	Ductal hyperplasia	02	02
4.	Ductal carcinoma in situ	08	08
5.	Invasive ductal carcinoma	54	54
6.	Invasive lobular carcinoma	16	16
	Total number of cases	100	100

Out of the 100 cases studied a maximum of 54 cases were of invasive ductal carcinoma, followed by invasive lobular carcinoma 16, fibroadenoma 146 ductal carcinoma in situ 08, fibrocystic disease 04, and ductal hyperplasia 02.

Age-wise distribution of benign cases in the present study showed a majority of cases 12(54.5%) occurring between 21-30 years of age, followed by 06 cases (27.3%) in the age group 31-40 years and 03 cases (13.6%) seen in <20 years of age and 01 cases (4.6%) in the age group 41-50 years.

Age-wise distribution of malignant cases in the present study showed a majority of cases 36(46.2%) occurring between 41-50 years of age followed by 32 cases (41.0%) in the age group >50 years and 10 cases (12.8%) seen in females of 31-40 years of age.

Table 3: Histological tumour subtypes and tumor grade

Histologic Type (No. of cases)	Grade I	Grade II	Grade III
Fibroadenoma (16)	-	-	-
Fibrocystic disease (4)	-	-	-
Ductal hyperplasia (2)	-	-	-
Ductal carcinoma in situ (8)	-	-	-
Invasive ductal carcinoma (54)	09	33	12
Invasive lobular carcinoma (16)	12	04	-

All invasive carcinoma were graded using The Elston/Nottingham modification of the Bloom-Richardson grading system. Most of the cases seen were of grade ll

Table 4:Scoring Of E-Cadherin Immunostain in Histologic Tumor Subtype

Histologic Type (No. of cases)	Positive E-cadherin (+3)	Positive E-cadherin (+2)	Negative E-cadherin (+1)	Negative E-cadherin (0)
Fibroadenoma (16)	14	-	-	-
Fibrocystic disease (4)	6	-	-	-
Ductal hyperplasia (2)	2	-	-	-
Ductal carcinoma in situ (8)	5	3	-	-
Invasive ductal carcinoma (54)	09	15	12	18
Invasive lobular carcinoma (16)	-	-	-	16

Benign lesions: Positive E-cadherin expression was seen in all 22(100%) cases of benign breast lesions. **Malignant lesions:** Positive E-cadherin expression was seen in all 08(10.3%) cases of ductal carcinoma in situ and 24 (44%) cases of invasive ductal carcinoma. Of 16 invasive lobular carcinomas with the classic histologic pattern, (100%) showed complete loss of E-cadherin.

Table 5: Correlation between E-cadherin intensity and histological grade of invasive ductal carcinoma

Histological grade	0 EC Intensity	+1 EC Intensity	+2 EC Intensity	+3 EC Intensity	Total Cases (%)
Grade I	-	-	06	03	09(16.7%)
Grade II	09	09	09	06	33(61.1%)
Grade III	09	03	-	-	12(22.2%)
Total and %	18(33.3%)	12(22.7%)	15(27.3%)	09(16.7%)	54(100%)

Invasive ductal carcinoma: correlation between E-cadherin intensity and histological grade of invasive ductal carcinoma showed positive expression in 24 (44%) cases of invasive ductal carcinoma. E-cadherin expression was present in 100% of tumor cells in all positive cases

And the staining was +2 in 15 cases and +3 in only 09 cases. Associated Ductal carcinoma in situ was positive with +3 E-cadherin immunoreactivity**.**

Table 6: Evaluation of e-cadherin immune-reactivity in benign vs malignant lesions of the breast

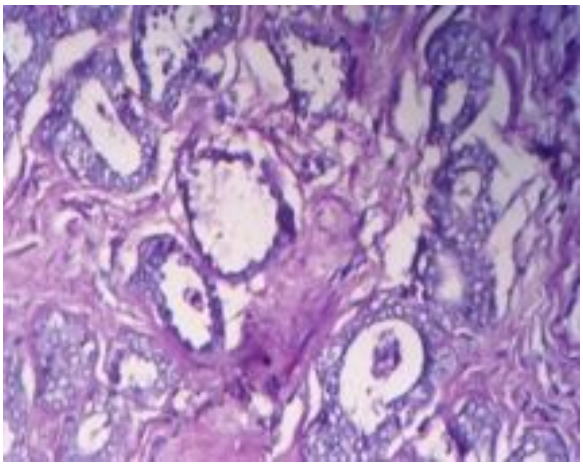
Type of Breast lesion	E-cadherin positive(+3, +2)	E-cadherin Negative(+1, 0)	Total	'P' value (using Fisher exact test)
Benign	22	00	22	<0.0001 (Highly significant)
Malignant	32	46	78	

The result was analysed by Fisher's exact test. E-cadherin positivity was seen in all benign lesions 22(100%) and among malignant lesions 32(41.0%) cases were positive and 46(59.0%) were negative. Thus a highly significant association was found (p-value **<0.0001**).

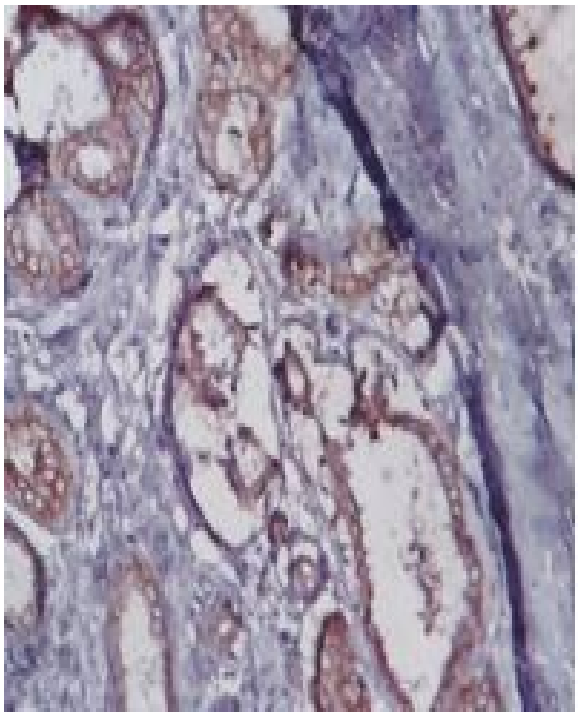
Table 7: Evaluation of E-cadherin immunoreactivity in lobular vs ductal carcinoma

Type of Carcinoma	E-cadherin positive(+3, +2)	E-cadherin Negative(+1, 0)	Total	'P' value (using Fisher exact test)
Lobular carcinoma	00	16	16	0.0006 (significant)
Ductal carcinoma	24	30	54	

In all lobular carcinoma cases, 16(100%) were negative and among ductal carcinoma cases, 24(44%) were positive and 30(56%) were negative. The result was analysed by Fisher's exact test. This association was found to be significant with a p-value < **0.0006**.

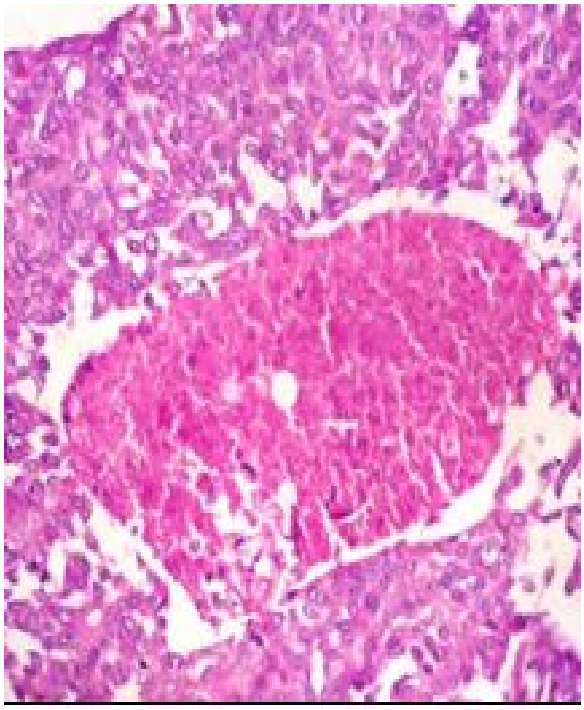


Microphotograph 1: H&E stained section of fibroadenoma showing glandular and stromal proliferation (Pericanalicular pattern). (400X)



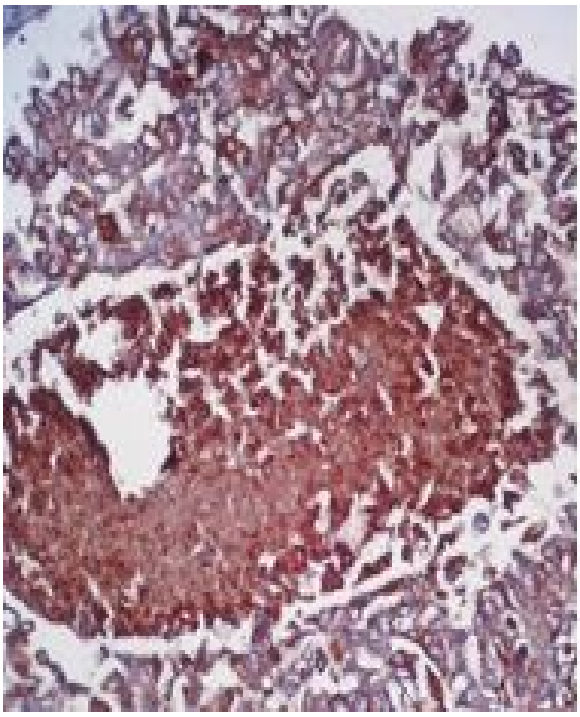
Microphotograph 2:

Microphotograph of immunohistochemical staining of E-cadherin in fibroadenoma (Pericanalicular pattern) showing (+3) membranous positivity. (400X**)**



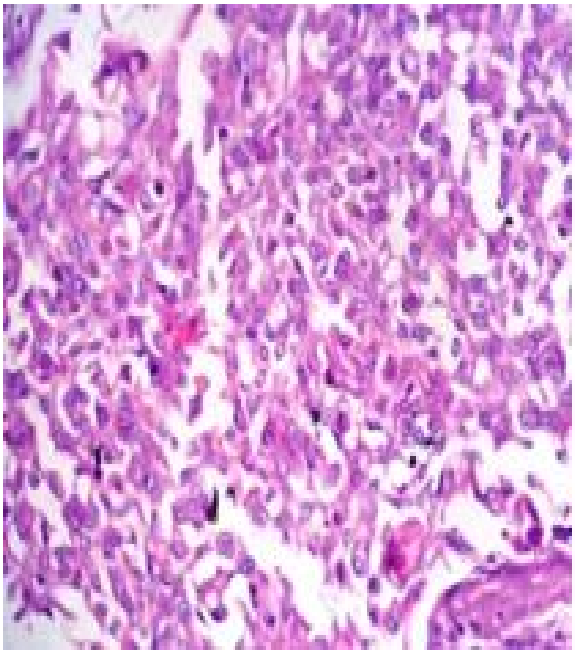
Microphotograph 3

H&E stained section of ductal carcinoma in situ with Comedopattern



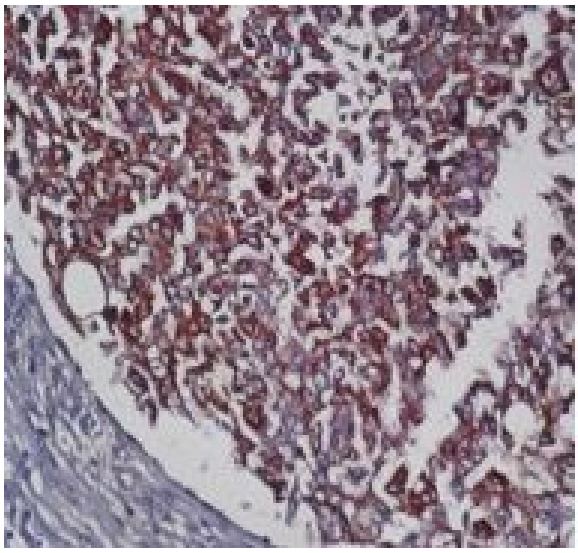
Microphotograph 4

Immunohistochemical staining of E-cadherin in ductal carcinoma in situ with comedo pattern showing strong membranous positivity. (400X)



Microphotograph 5

H&E stained section of invasive ductal carcinoma. Individual tumor cell shows pleomorphism, mitotic activity, hyperchromasia and prominent nucleoli. (400X)



Microphotograph 6: Immunohistochemical staining of invasive ductal carcinoma showing strong (+3) membranous positivity. (400X)

Discussion

A. Khemka et al found fibroadenoma the most common benign lesion 29/37 (78.4%) followed by cases of fibrocystic disease 4/37(10.4%) [18]. Vishal G. Mudholkar et al documented fibroadenoma as the most common lesion 111/127 (87%) among all benign breast neoplasms [19]. Alexandre et al also documented fibroadenoma as the most common benign lesion (19/42) in their study [20]. In the present study out of 78 malignant cases, the maximum number of cases were of invasive ductal carcinoma 54/78 (69.2%) followed by cases of invasive lobular carcinoma 16/78 (20.5%) and ductal carcinoma in situ 08/78 (10.3%). Lee et al observed invasive ductal carcinoma (76%) as the most common breast malignancy followed by invasive lobular carcinoma (11%) [21]. Bane et al (found (85%) of cases of invasive ductal carcinoma were followed by invasive lobular carcinoma (7%). A similar finding was documented by Vishal G. Mudholkar according to the most common type of carcinoma invasive ductal carcinoma (88%) [19]. In the present study (FIGURE-1) majority of benign cases 12 (54.5%) occurring in between 21-30 years of age, followed by 06 (27.3%) cases in the age group 31-40 years, 03 (13.6%) cases in less than 20 years of age and 01 (4.6%) case in the age group 41-50 years. Mahua Choudhry et al observed that benign lesions of the breast were more commonly seen in younger age groups

With a maximum of 44.1% of patients in the 21-30 years of age group [22]. Reeni Malik et al also observed similar findings[23]. In the present study (FIGURE-2), the maximum number of malignant cases was 36 (46.2%) occurring between 41-50 years of age followed by 32 (41.0%) in the age group above 50 years of age and 10 (12.8%) seen in 31-40 years of age. Our findings are in accordance with the observation of Kurubasree Lakshmi and A. Khemka et al according to the maximum number of breast malignancies seen in the age group 41-50 years of age [18, 24]. In the present study out of a total of 70 cases of invasive breast carcinoma, 54 (77.1%) cases were of invasive ductal carcinoma and 16 (22.9%) cases were of invasive lobular carcinoma. Histological grading after the final histologic review of all invasive carcinoma using Elston/Nottingham modification of Bloom-Richardson system according to Bane et al showed that (Table-3) a maximum number of cases of invasive carcinoma 37/70 (52.9%) seen were of grade II, followed by 21/70 (30.0%) cases of grade I and 12/70 (17.1%) cases of grade III [25]. Marwa Elshaer graded 26 cases of invasive breast carcinoma cases and observed that the maximum number of cases were of grade II 12/26 (46.2%), followed by 10/26 (38.5%) cases of grade I and grade III 04/26 (15.3%) cases in their study [27]. Vishal G Mudholkar et al graded 106 cases of malignant breast neoplasm and observed grade II invasive breast carcinoma was the most common (54.49%) [19]. In the present study on assessing E-cadherin immunoreactivity score (Table-4), all benign lesions (22) which included fibroadenoma, fibrocystic disease, and ductal hyperplasia showed that all cases were strongly positive (+3). Among all the malignant lesions (78) which included invasive ductal carcinoma, invasive lobular carcinoma and ductal carcinoma in situ, 32 cases were positive (+3,+2) and 54 cases were negative (+1,0) for E-cadherin immunoreactivity.On analyzing the correlation between E-cadherin intensity and histological grade of invasive ductal carcinoma (Table-5), E-cadherin expression was present in tumour cells in all positive cases and the staining was +2 in 15 (27.3%) cases and +3 in only 09 (16.7%) cases. All ductal carcinoma in situ lesions were positive with +3 E-cadherin immunoreactivity. Of 16 invasive lobular carcinoma cases with a classic histological pattern, (100%) showed complete loss (0) of E-cadherin.A similar finding was observed by Marwa Elshaer selected 11 cases of nonmalignant breast lesions including fibroadenoma, ductal papilloma and lobular hyperplasia in their study and observed E-cadherin positivity in all the cases with E-cadherin score +3 in fibroadenoma, ductal papilloma and score +2 in lobular hyperplasia [26]. Strong E-cadherin expression was also demonstrated by Bukholm et al in the normal ductal and acinar epithelium as well as in ductal hyperplasia. The immunoreactivity pattern of E-cadherin in benign lesions in the present study is in accordance with the above studies [27]. Marwa Elshaer selected 38 cases of malignant breast lesions including invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, lobular carcinoma in situ and tubular carcinoma in their study and observed 17 cases positive (+3, +2) and 22 cases of negative (+1, 0) for E-cadherin. Positive E-cadherin expression was seen in 12/18 (66.7%) cases of invasive ductal carcinoma. All 08 cases of invasive lobular carcinoma showed complete loss of E-cadherin [26]. Hina S. Qureshi et al studied E-cadherin expression in 204 cases of invasive ductal carcinoma and 49 cases of invasive lobular carcinoma. Positive E-cadherin expression (+3, +2) was seen in 203/204 (99.5%) cases of invasive ductal carcinoma. Of 49 invasive lobular carcinoma cases with the classic histologic pattern, 44 (90%) complete loss of E-cadherin. The expression of E-cadherin in malignant lesions in our study is in accordance with the above studies [28]. On the statistical analysis of E-cadherin expression in benign and malignant lesions of the breast by Fisher exact test highly significant association was seen with p-value <0.0001(Table-6). Analyzing E-cadherin staining in invasive ductal carcinoma and invasive lobular carcinoma revealed a statistically significant difference between the group with a p-value of 0.0006(Table-7). Overall, negative staining of E-cadherin in invasive lobular carcinoma was specific for the diagnosis of invasive lobular carcinoma. Marwa Elshaer revealed a statistically highly significant difference between invasive ductal carcinoma, invasive lobular carcinoma, and tubular carcinoma (p-value <0.001) [26]. Hina S. Qureshi et al also revealed a highly statistically significant difference ($p < 0.001$) in the comparison of E-cadherin staining between invasive ductal carcinoma, invasive lobular carcinoma, and invasive lobular carcinoma variants [28].

Conclusion

1. On analyzing the immunoreactivity pattern of E-cadherin in various benign breast lesions including fibroadenoma, fibrocystic disease, and ductal hyperplasia showed strong (+3) membrane positivity in all 22 (100%) cases.

2. Analyzing the immunoreactivity pattern of E-cadherin in various malignant breast lesions showed moderate to strong (+3,+2) membrane expression in 44% of cases of invasive ductal carcinoma and strong (+3) membrane expression in 100% of cases of ductal carcinoma in situ. Reduced expression of E-cadherin expression in 60% of cases was seen mainly associated with poor differentiation and high tumour grade.

3. On analyzing the immunoreactivity pattern of E-cadherin in invasive lobular carcinoma complete loss (0) was found in 100% of cases.

4. On analyzing the p-value for E-cadherin immunoreactivity in benign and malignant lesions highly significant association was found (p-value <0.0001).

5. On analyzing the p-value for E-cadherin immunoreactivity in invasive lobular carcinoma Vs invasive ductal carcinoma significant association was found (p-value < 0.0006).

The present study demonstrates that E-cadherin is strongly expressed in all benign breast lesions and there is increasing loss of E-cadherin expression with increasing grade/severity of malignancy. Thus it is a useful marker for differentiating benign and malignant lesions. There is variable loss of this marker in invasive ductal carcinoma and total loss in invasive lobular carcinoma. Hence it suggests that E-cadherin is a marker of choice for the diagnosis of Invasive lobular carcinoma and it may be involved in the pathogenesis of this form of breast cancer.

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