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DETECTION OF EPITHELIAL CADHERIN IMMUNOEXPRESSION AMONG SUDANESE FEMALES WITH BREAST CANCER

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ABSTRACT

Background: Breast cancer continues to be a major cause of morbidity and mortality among Sudanese female population due to lack of education and efficient screening programs. Different parameters have been investigated to predict the prognosis in breast cancer; but still far from optimistic. E-cadherin is a novel prognostic marker which is a calcium-dependent epithelial cell adhesion molecule. Its loss has been associated with metastases, thereby plays a major role in histological grading of the cancer. The prognostic value of E-cadherin in breast cancer has been studied for years, yet results remain controversial. **Aim:** This study aimed to detect immunoexpression of E-cadherin in breast cancer tissues, and also to correlate expression of E-cadherin with tumor grade and patients age and to evaluate the prognostic and metastatic values of E- cadherin in breast cancer. **Materials and methods:** This was a descriptive cross sectional study conducted in Khartoum state-Sudan during period from December to July 2018. Forty three formalin fixed paraffin embedded (FFPE) tissues were included in this study; 39 tissues from patients with invasive ductal carcinoma and 4 tissues with invasive lobular carcinoma, were subjected to detect immunoexpression of E-cadherin in breast cancer tissues. **Results:** E-cadherin was lost in 79.1% expressed in 20.9% of cases (N=43). 82.1% of cases with Invasive Ductal Carcinoma (IDC) were showed negative expression (=39), 50% of cases with ILC were showed negative expression. E-cadherin (score zero and one) was observed in tumors with higher grades, E-cadherin (score zero and one) was more frequently observed in tumors with positive lymph node metastasis and vice versa. **Conclusion:** E-cadherin was lost in the majority of tissues, also was lost gradually with the progression of tumors and metastasis, there was statistically significance different with tumor grades but not with metastasis.

KEYWORDS: E-cadherin, Breast cancer, IDC, ILC, TMA, Sudan.

ABBREVIATION

Abbreviations	Meaning
DAB	3,3'-Diaminobenzidin
DPX	Disterene a plasticizer and xylene
D.W	Distiller eater
E-cadherin, E-CD	Epithelial cadherin
EDTA	Ethylenediaminetetraacetic acid
FFPE	Formalin fixed paraffin embedded
HRP	Horseradish peroxidase
H&E	Haematoxylin and eosin
IDC	Invasive Ductal carcinoma
IHC	Immunohistochemistry
ILC	Invasive lobular carcinoma
P	Probability
PBS	Phosphate buffer saline
PhD	Doctor of philosophy
RT	Room temperature

r	Correlation coefficient
R.T.W	Running tap water
SPSS	Statistical package for the social sciences
TMA	Tissue micro array
TWIST	Twist – related protein 1 (TWIST1)

INTRODUCTION

The cancer of the mammary gland (cancer of the breast) is a malignant tumor that come from the breast epithelium cells, and spread into near structures.[1] It's the usual cancer among females over the world. There are 1.67 million new women investigated with the cancer of the breast every year representing (25% of all malignant tumors) often lethal, it was the leading cause of cancer deaths. Medications of this cancer are available both radical, surgery (mastectomy), and the prognosis of this cancer is still far from optimistic.[2]

The first step in the metastatic cascade of cancer is loss of cellular adhesion, epithelial cadherin (E-cadherin) serves as intracellular glues, and their cytoplasmic portions connected to beta catenin adjacent E-cadherin molecules keep the cells together however E-cadherin can transmit growth inhibiting signals by separating beta catenin. E-cadherin function is lost in almost all epithelial cancers, either by mutational inactivation of E-cadherin gene, activation of beta catenin gene or by insufficient expression of the Zinc finger protein SNA1 (SNAIL) and Twist – related protein1 TWIST1 or (TWIST) transcription elements that inhibit E-cadherin expression.[3] according to the fact that selective loss of E-cadherin can cause dedifferentiation and invasiveness in human breast carcinomas, leading E-cadherin to be classified as tumor suppressor gene so the loss of E-cadherin expression has been investigated in invasive lobular carcinoma of the breast, but the relevance between E-cadherin expression and breast cancer histopathology and prognosis still inconspicuous.[4]

MATERIALS AND METHODS

This was a descriptive cross section study. The study population consisted of 43 Formalin Fixed Paraffin Embedded tissues (FFPE) samples from Sudanese females with breast cancers were included in this study as case group. This study was performed during period from December 2017 to July 2018.

Sample processing

The study included 27 FFPE tissues with IDC assembled in one tissue microarray (TMA). The study also included 16 non TMA FFPE tissues, 4 of them with ILC, the remainders 12 were with IDC. The Haematoxylin & Eosin (H&E) staining method was applied to all sections, then were reviewed by an experienced histopathologist to include represented samples and area for TMA, and to exclude the non-represented samples, and to identify different histopathological features and to ensure that the preceding sections contained representative tissues for IHC.

TMA method

Using conventional mechanical pencil tips; a hollow needle was used to remove tissue cores as small as 1 mm in diameter from regions of interest in FFPE tissue samples. These tissue cores were then inserted in a recipient paraffin block in a precisely spaced array pattern. then the array block was covered by microscopic glass slide, after that introduced into dry oven at 37 ^{0}C until the block was warmed, then the slide was rotated over the cores, then let to cool at room temperature (RT), then incubated in the refrigerator freezer for complete solidification, then the TMA block was ready for sectioning.

Microtomy

Four µm thick sections were cut from conventional and TMA blocks by using a rotary microtome (MR22150-K2258-1124 Histoline- Italy). The sections were taken from the water bath (LAB TECK, 009222- India) immediately after they have stretched out, sections were placed on a super frost positive charge glass slide. The incubation time of the sections in water bath was 5 seconds; then the slides were placed in a slide holder for drying at room temperature (RT) overnight. Then slides were incubated in dry oven at 65-70 °C for 20-40 min and then stained immunohistochemically.

Methods of detection

H & E staining method

Paraffin sections were dewaxed in xylene for 10 minutes, then hydrated through descending grades of alcohol to water, after that stained with Mayer's Haematoxylin for 7 min, washed well in running tap water until sections were blued for 5 min, each blued section was counterstained in 1% eosin for 3 min, washed in running tap water for 1 min, dehydrated in ascending grades of alcohol, dehydration was completed by air. The dehydrated sections were cleared in xylene, mounted in Disterene a plasticizer (polystyrene) and xylene (DPX). All mounted sections were examined using Olympus microscope (CX21FS1, Olympus Corporation, Tokyo-Japan).

Immunohistochemistry (IHC) methods

Sections for IHC technique were stained according to the manufacture instructions (Zytomed Systems, Germany), section for IHC technique were stained in histopathology lab at Army Hospital-Omdurman city at Khartoum state-Sudan and diagnosed by the investigators and reviewed at Histopathology lab at Sharq Elneil College-Khartoum North-Sudan by well-trained PhD. Medical laboratory histopathologist.

Sections were deparaffinized in two changes of xylene for 10 minutes in each change, then rehydrated in descending changes of ethanol as followed; sections were placed in two changes of absolute ethanol for 5 minutes in each change and then were placed in 90% ethanol for 3 minutes, and then placed in 70% ethanol for 2 minutes, then washed in distilled water for 2minutes and washed two times in Phosphate Buffer Saline (PBS). After Rehydration antigens were retrieved in preheated water bath at 95^{o}C in plastic coplinjar contained EDTA buffer pH (9.0) for 40 minutes. After antigen retrieval, slides were washed in PBS of pH 7.4 for 3-5 minutes, then endogenous peroxidase activity was blocked in 3% hydrogen peroxide block for 10-15 minutes, then slides were washed in PBS for 3-5 minutes and then blocking solution was applied to each section for 5 minutes at room temperature to block nonspecific background staining, then slide was washed in PBS for 2 minutes, then ready use specific primary antibody to E-cadherin (Rabbit anti -E- cadherin-cat. NO.: BRB047) was applied to each section for 30-60 minutes, then slides were washed in PBS 3-5 minutes, then the second layer antibody HRP step polymer anti mouse/ rabbit/ rat was applied for 30 minutes at room temperature, the slides then were washed in PBS for 3 minutes. After that 1 drop (40 micro liters) from 3.3 diaminobenzidine tetrahydrochloride (DAB) plus Chromogen added to 1 ml of DAB plus substrate, mixed by swirling and applied to tissue for 5-15 minutes, then slides were rinsed in distilled water (DW) to stop the reaction, then slides were counter stained in Mayer's Haematoxylin for 2 minutes, blued in RTW for 3 minutes, dehydrated in ascending grades of ethanol, cleared in xylene and mounted in DPX. Then slides were examined under the microscope.

Interpretation of IHC staining results

Negative staining achieved when no crisp brown staining was observed in the cytoplasm and/or cell membrane of the target malignant cells (score is 0 and over expression assessment is negative). Observed cytoplasm and/ or membrane staining less than 10% of tumor cells regarded also as negative (score is 0 and over expression assessment is negative). A faint/barely perceptible cytoplasm and/or cell membrane staining was detected in more than 10% of tumor cells and incomplete membranous staining regarded also as negative (score is 1+ and over expression assessment is negative). A weak to moderate complete cytoplasmic and/or cell membrane staining was observed in more than 10% of tumor cells regarded as weakly positive (score is 2+ and over expression is weakly positive). A strong complete cytoplasmic and/or cell membrane staining was observed in more than 10% of tumor cells regarded as positive (score is 3+ and over expression assessment is positive).[5]

Quality control

For H & E staining technique all quality issues and precautions were carried out as Theory and Practice of Histological Techniques.[6] For IHC positive and negative control sections were used to evaluate the working solutions and to evaluate the tested slides. All precautions and quality issues were obtained as manufacture instructions (Zytomed Systems, Germany).

Statistics

All obtained results and data were analyzed by Statistical Package for the Social Sciences (SPSS) version 22.0 and Excel computerized program (windows 7). Pearson's chi-square and correlation coefficient (r) tests were used to assess the inter group significance. Other variables, frequencies and percentages were calculated for comparison and presented in form of figures and tables. The p value was used to assess the result significance, regarded as significant results (p value)> 0.05, correlation test was used to confirm the correlations between variables, correlation coefficient (r) obtained where the (r) value (0.0) regarded as no correlation, r (0.0-0.25) regarded as weak correlation, r (0.25-0.75) regarded as moderated correlation, r (0.75 -1) regarded as strong correlation.

RESULTS

The age of patients was ranged from 25-70 years old with the average mean of age 50 years old. The age of patients sub grouped into three groups, group one included patients with 25-45 years old (pre-menopausal), group two with 46-65 years old (menopausal), the last age group of those with age equal or more than 65 years old (advanced menopausal).

Grade 1 of tumor comprised 5.3%, grade 2 comprised 36.8%, and grade 3 comprised 57.9% of samples, N=38. Lymph nodes metastasis was observed in 77.70%, the non- metastasis was detected in samples 22.2%, N=27.

The E-cadherin expression among study populations was as followed; the negative expression was detected in 48.8%, the weakly positive expression was detected in 30.2%, while positive expression was detected in 20.9%, N=43. The E-cadherin expression score was as followed; score (0) was detected in 11.6%, score (1) was detected in 37.2%, score (2) was detected in 30.2% and score (3) was detected in 20.9%, N=43.

Regarding correlation between E-cadherin expression and tumor subtypes, our results showed that; the negative, weakly positive and positive expression was detected in 51.3%, 30.8%, and 17.9% samples respectively out of 39 IDC. The negative, weakly positive and positive expression was detected in 25%, 25%, and 50% samples respectively out of 4 ILC. The p value was 0.166; correlation coefficient (r) was 0.215 as indicated in (table 1).

Regarding correlation of E-cadherin immunoexpression with tumor grades, our results revealed that; the negative expression was detected in 1out of 2 samples in grade1, 5 out of 14 samples in grade 2 and 14 out of 22 samples in

grade 3. The weakly positive expression was detected in (0.0) out of 2 samples in grade 1, 5 out of 14 samples in grade 2 and 7 out of 22 samples in grade 3. The positive expression was detected in 1 out of 2 samples in grade 1, 4 out of 14 samples in grade 2 and 1 out of 22 samples in grade 3. The p value was 0.039, the correlation coefficient (r) (-0.336), as showed in (table 2).

Regarding comparison of E-cadherin expression with the age of patients, our results showed that; the negative expression was detected in 6 out of 14 premenopausal patients, 11out of 18 menopausal patients and 3 out of 8 advanced menopausal patients. The weakly positive was detected in 7 out of 14 premenopausal patients, 3 out of 18 menopausal patients and 2 out of 8 advanced menopausal patients. The positive expression was detected in 1 out of 14 premenopausal patients, 4 out of 18 menopausal patients and 3 out of 8 advanced menopausal patients. The p value was (0.180) as illustrated in (table 3).

Regarding comparison of E-cadherin expression with metastases to the lymph nodes, negative E-cadherin expression was detected in 12 out of 21 tissues with positive metastasis to lymph nodes, 3 out of 6 tissues with negative metastasis to lymph nodes. The weakly positive was detected in 8 out of 21 tissues with positive metastasis to lymph nodes, 3 out of 6 tissues with negative metastasis to lymph nodes. The positive expression was detected in 1 out of 21 tissues with positive metastasis to lymph nodes, (0.0) out of 6 tissues with negative metastasis to lymph nodes. The p value was (0.782), as showed in (table 4).

Regarding comparison between E-cadherin expression scores with tumor grades, score (0.0) was recorded in 1 out of 2 samples in grade 1, 1 out of 14 samples in grade 2 and 3 out of 22 samples in grade3, the score 1 was observed in (0.0) out of 2 samples in grade 1, 4 out of 14 samples in grade 2 and 11 out of 22 samples in grade 3, the score 2 was detected in (0,0) out of 2 samples in grade 1, 5 out of 14 samples in grade 2 and 7 out of 22 samples in grade 3, the score 3 was present in 1 out of 2 samples in grade 1, 4 out of 14 samples in grade 2 and 1 out of 22 samples in grade 3. The p value was (0.139), as indicate in (table 5).

Regarding correlation of E-cadherin expression scores with cancer metastases to the lymph nodes, score (0.0) was detected in 2 out of 21 metastases lymph nodes samples, (0.0) out of 7 non lymph nodes samples, the score 1 was found in 9 out of 21 metastasis lymph nodes samples, 4 out of 7 non lymph nodes metastases samples, score 2 was detected in 8 out of 21 metastases lymph nodes samples, 3 out of 7 non lymph nodes metastases samples. The score 3 was observed in 2 out of 21 lymph nodes metastases samples, (0.0) out of 7 non lymph nodes metastases samples. The p value was (0.661), the correlation coefficient (r) (-0.028), as showed in (table 6).

Table (1): Correlation of E-cadherin expression with breast cancer subtypes.

	Cancer type	E-cadherin expression			Total	P value	Correlation coefficient (r)
		Negative	Weakly positive	positive			
	IDC	20	12	7	39	0.166	0.215
	ILC	1	1	2	4		
Total		21	13	9	43		

- Chi square test
- Power of significance is 0.05.

Table (2): Correlation of E-cadherin expression with tumor grades.

	Tumor grades	E-cadherin expression			Total	p. value	Correlation coefficient (r)
		Negative	Weakly positive	positive			
	Grade 1	1	0	1	2	.039	-0.336
	Grade 2	5	5	4	14		
	Grade 3	14	7	1	22		
Total		20	12	6	38		

- Chi square test
- Power of significance is 0.05.

Table (3): Comparison between E-cadherin expressions with age of Patient's.

	Patient's age	E-cadherin expression			Total	p. value
		Negative	Weakly positive	positive		
	25-45	6	7	1	14	.180
	46-65	11	3	4	18	
	65<	3	2	3	8	
Total		20	12	8	40	

- Chi square test
- Power of significance is 0.05.

Table (4): Comparison between E-cadherin expression with metastases to lymph nodes.

	Cancer metastases	E-cadherin expression			Total	p. value
		Negative	Weakly positive	positive		
	Lymph nodes metastases	12	8	1	21	0.782
	Non lymph nodes metastases	3	3	0	6	
Total		15	11	1		

- Chi square test
- Power of significance is 0.05.

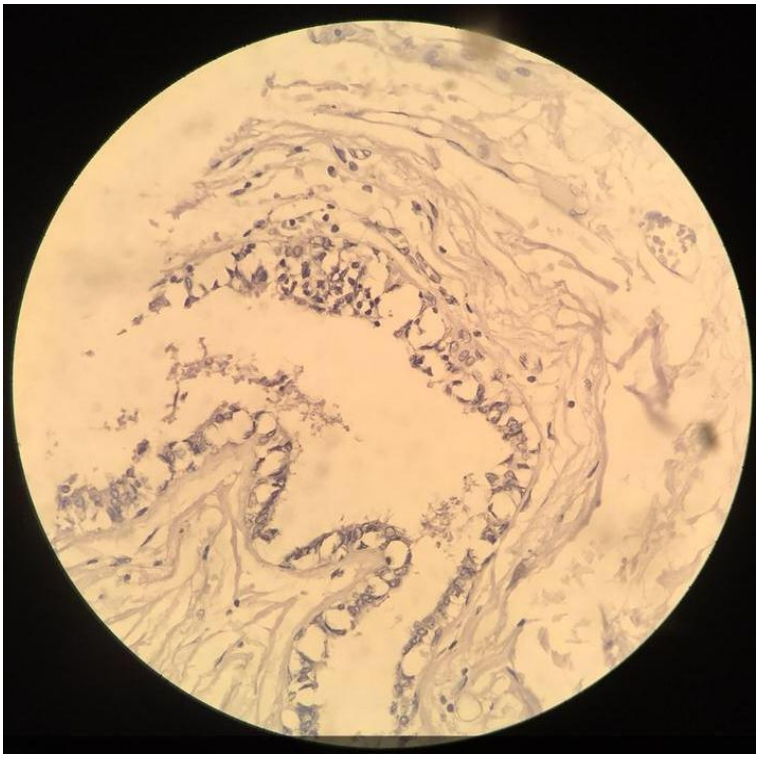
Table (5): Comparison between E-cadherin expression scores and tumor grades.

	Tumor grade	E-cadherin expression scores				Total	p. value
		Score 0.0	Score 1	Score 2	Score 3		
	Grade 1	1	0	0	1	2	0.139
	Grade 2	1	4	5	4	14	
	Grade 3	3	11	7	1	22	
Total		5	15	12	6	38	

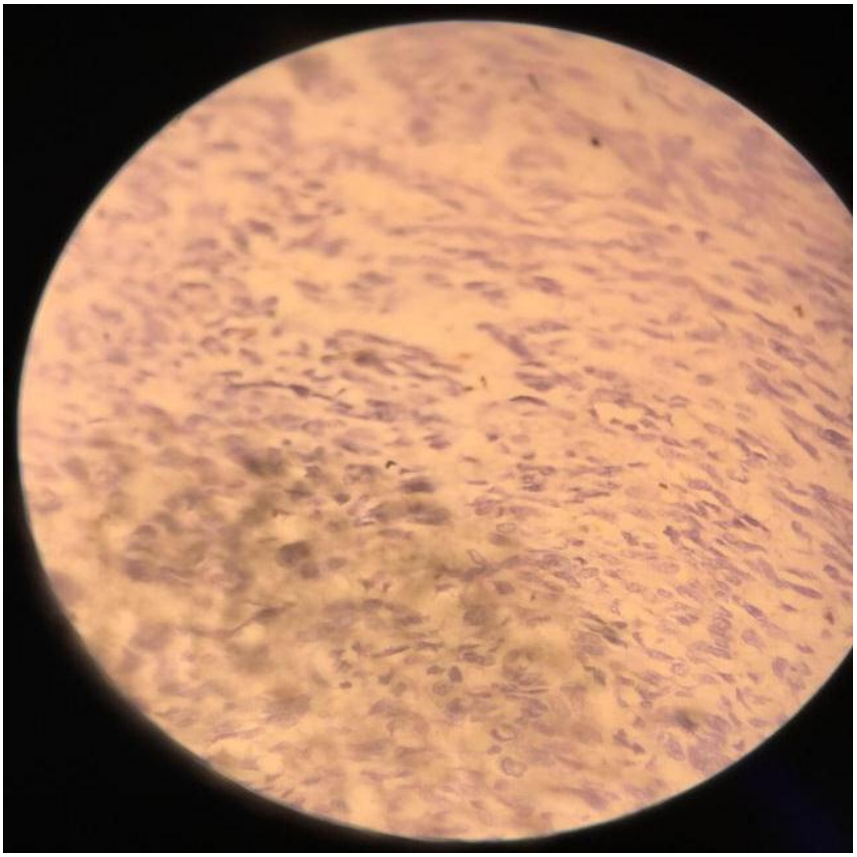
- Chi square test
- Power of significance is 0.05.

Table (6): Correlation between E-cadherin expression scores with tumor metastases.

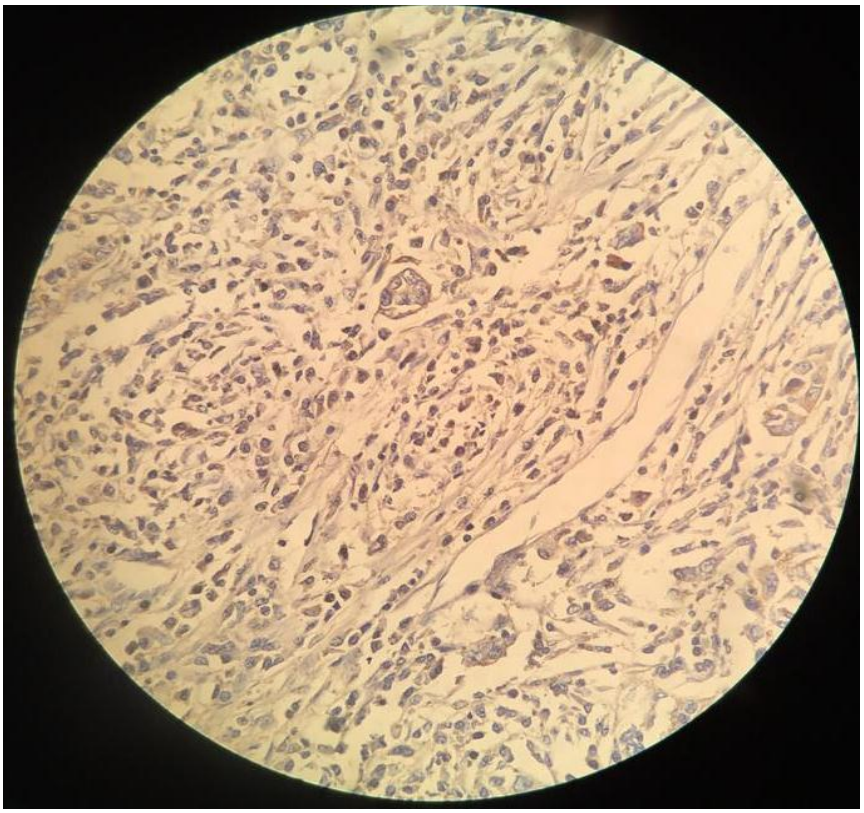
	Cancer metastases	E-cadherin expression scores				Total	p. value	Correlation coefficient (r)
		Score 0.0	Score 1	Score 2	Score 3			
	Lymph nodes metastases	2	9	8	2	21	0.661	-0.028
	Non lymph nodes metastases	0	4	3	0	7		
Total		2	13	11	2	28		



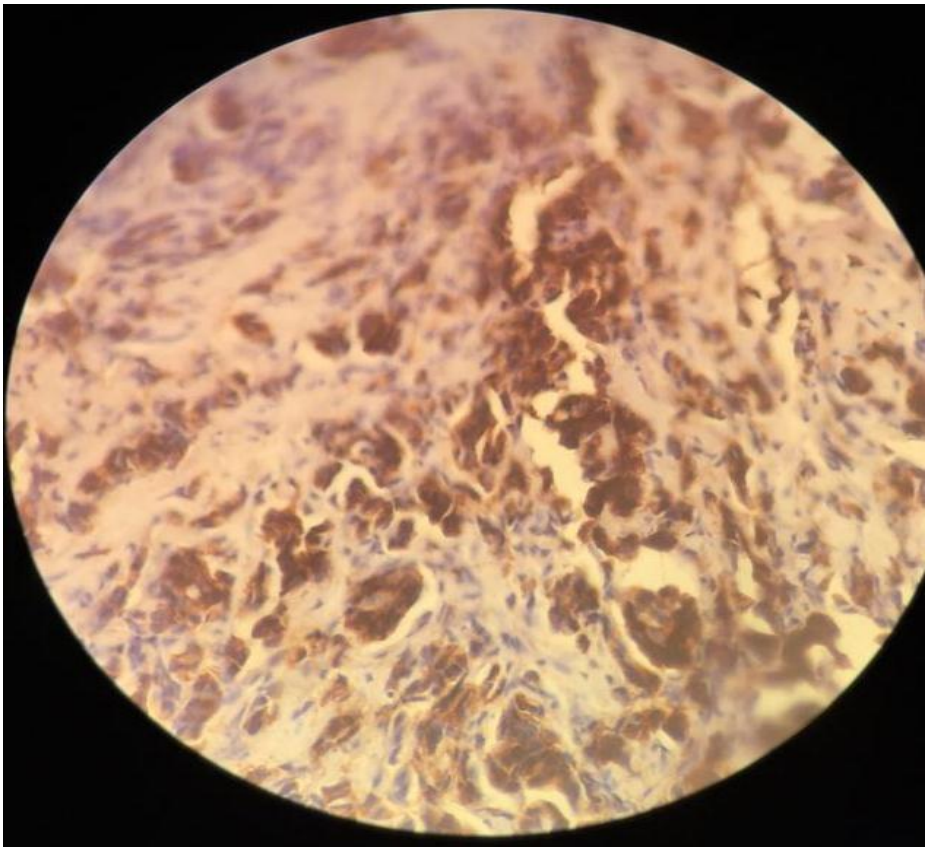
E-cadherin staining x40 of grade 3 invasive ductal carcinoma showing negative expression (score 0.00).



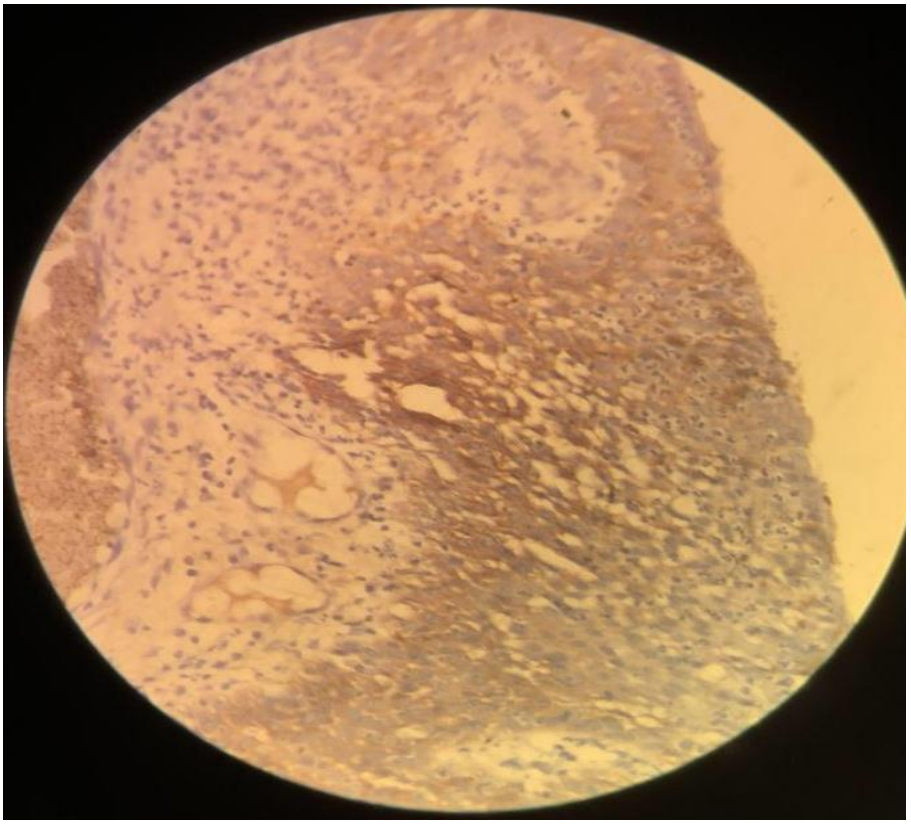
E-cadherin staining x40 of grade 2 invasive ductal carcinoma showing negative expression (score 0.00).



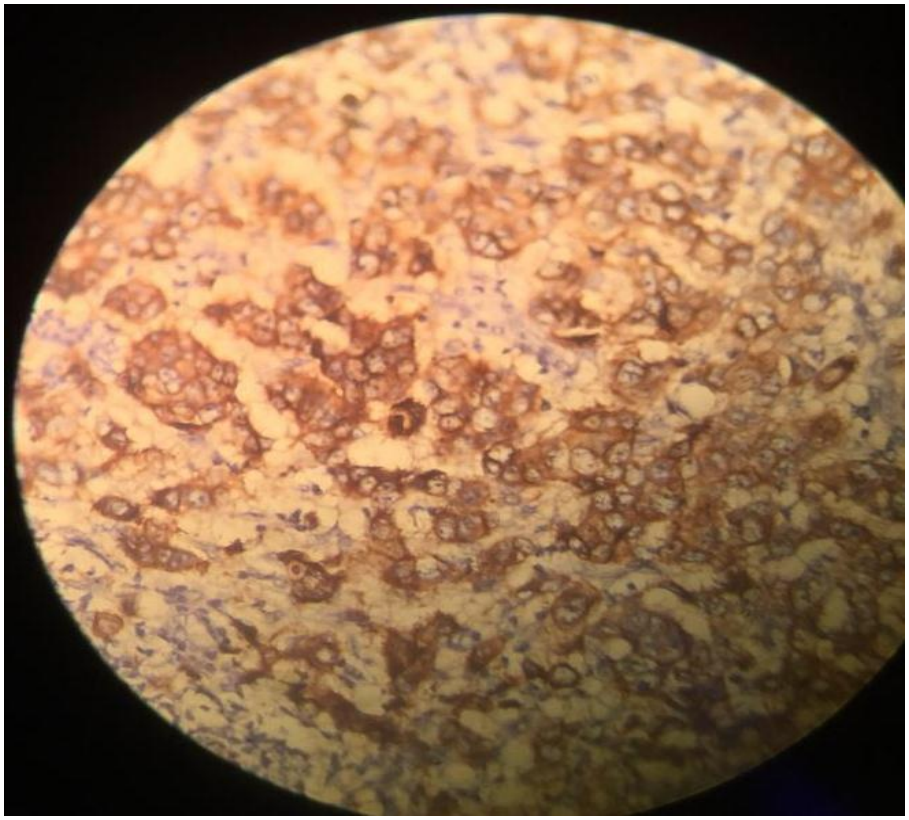
E-cadherin staining x 40 of grade 3 invasive ductal carcinoma showing negative expression (score 1) cytoplasmic-membranous.



E-cadherin staining x 40 of grade 2 invasive ductal carcinoma showing positive expression (score 2) cytoplasmic-membranous.



E-cadherin staining x 40 of grade 2 invasive lobular carcinoma showing positive expression (score 2) cytoplasmic-membranous.



E-cadherin staining x 40 of grade 3 invasive lobular carcinoma showing positive expression (score 3) cytoplasmic-membranous.

DISCUSSION

Many immunohistochemical studies have examined changes in expression of the E-cadherin gene in human malignancies. In almost all non- colonic tumors examined, the patterns of changes in the expression is positively correlated to loss of tumor differentiation. Loss of E-cadherin expression has been correlated with a high grade and advanced stages of disorder, and with poor prognosis.

The current study showed that; the most of breast cancer patients were in the menopausal age followed by younger adult women and severe menopausal women respectively, and this may be due to the fact that women usually present late with disease; the age of patients in this study match with that study conducted in our country by Ali and Faiza, they summarized that among one hundred and eighty patients files were collected and reviewed, 47.3% were in the age between 50 and 80 years old[7], also our results agree with Carey *et al*., who summarized that; 7% of females with carcinoma of the breast are estimated before the age 40 years old and this cancer account above than 40% of all malignant tumors in females with age group 40 years old[8], our results partially similar to that study conducted by Fadwa *et al*., in Pumped Scopus and Google Scholar most of patients are advanced ages most of our cancer patients are lies between more than 45 and less than 65, though they differs in that; 50% of their cancer patients are more than 65 years followed by 30% of patients are more than 70 years.[9]

The study conducted on 43 FFPE tissues previously diagnosed with breast cancers, 90.7% FFPE tissues with breast invasive ductal carcinoma and 9.3% FFPE with breast invasive lobular carcinoma involved as case groups.

Concerning the histological subtypes, our study showed that; invasive ductal carcinoma was predominant type over the invasive lobular carcinoma, similar results regarding histological findings was obtained by Laure and Patrick, they concluded that; the majority of invasive breast cancers are the invasive ductal carcinoma while just 10% are of invasive lobular type.[10]

Regarding tumor grading and cancer invasions, grade 3 was predominant grade followed by grade 2 and 1 consecutively, more than two thirds of samples recruited in this study were cancers that metastasize to the lymph nodes, and this is due to presentation of Sudanese women late in advanced stages of disease, our findings disagree with Luiten *et al*., they used mammography program, they concluded that; the majority of invasive breast cancers were low grade (45.4%) or intermediate grade (41.6%).[11]

Concerning E-cadherin immunoexpression and record scores among breast cancer, the negative (score 0 and score 1), weakly positive (score 2), and positive (score 3), the negative expression was higher followed by weakly positive and positive expressions respectively, this results similar to that obtained by Rajeev *et al*., they

concluded that; E-cadherin is expressed in most normal epithelial tissues, selective loss of E-cadherin can cause dedifferentiation and invasiveness in human carcinomas, leading E-cadherin to be classified as a tumor suppressor gene.[5]

Regarding the correlation of E-cadherin expression with breast cancer subtypes the higher percentages (50%) located in ILC, in contrast to the expression of IDC which showed lower expression (17.9%), but the calculated correlation coefficient (r) was weak and there was no statistical significant result as the p value was more than 0.05 (table 1), since most of our samples from high grades of the tumor, so our results similar to that obtained by Guilford who concluded that; loss of E-cadherin expression has been correlated with a high grade and an advanced stage of disorder, and with poor prognosis.[12] Our results regarding non- statistical significance of these results agreed with a study conducted by Ayda *et a*l., they concluded that; there is no statistical significant was found between E-cadherin expression and tumor subtypes[13], these results disagreed with Rajeev *et al*., who concluded that; statistical correlation of E-cadherin expression loss with a positive diagnosis of ILC was found, but there was no correlation with any prognostic tumor variable[5], also different result was obtained by Kanthilatha *et al*., they concluded that; highly significant correlation of the E-cadherin expression with histological phenotype of the breast cancer was present, as the p value was 0.0018.[14]

Regarding correlation of E-cadherin expression with tumor grade the higher frequencies descended from grade 3 to grade 1, our results showed strong significant association between the loss of E-cadherin expression and tumor grading as the p value was less than 0.05 (table 2), these finding agreed with those of Guilford and Rakha *et al*., they concluded that; E-cadherin expression was associated with a reduced disease, free interval , overall survival and also with indicators of poor prognosis including larger tumor size, higher histological grade.[12,15]

Unmatched results were achieved by Rajeev *et al*., and Ayda *et al*., they concluded that; there was no significant correlation was found between E-cadherin expression and tumor grading in ILC and IDC respectively.[5,13]

Regarding comparison between E-cadherin expression and patient's age, there was no statistical significant association (table 3), no published data that compare between E-cadherin expression and patient's age.

Concerning E-cadherin immunoexpression and breast cancer invasion to the lymph nodes, our results revealed that; the frequency of negative expression was higher in samples with metastases cancer to the lymph nodes than negative expression in samples with non-metastases to the lymph nodes, but with no significant association as the p value more than 0.05 (table 4), our results similar to that study conducted by Rakha *et al*.., who concluded that; E-cadherin expression was associated with a reduced disease, free interval, overall survival and also with indicators of poor prognosis including larger tumor size, higher histological grade, the development of distant metastasis and tumor negative for estrogen receptors with no association between E-cadherin expression and lymph node status was found, the negativity of E-cadherin expression and increased potential to lymph node metastasis.[15] Consistent results were obtained by Rajeev *et al*., and Gilford they concluded that; loss of E-cadherin associated with advance stages of breast cancer.[5,12]

Also similar results regarding the frequency of negative expression but not the p value was conducted by Madhavan *et al*., who concluded that; E-cadherin immunohistochemically in breast cancer showed significant down regulation in node positive tumors in comparison to node negative tumors.[16]

Concerning the correlation of E-cadherin expression score with tumor grade, our results showed that; the higher grade was with the lower score frequencies and lower grade with the higher score, but these results showed no significant association, as the p value more than 0.05 (table 5), there was no published data that correlate E-cadherin expression score with tumor grade.

Regarding the correlation of E-cadherin expression score with tumor metastases to the lymph nodes, our result showed that; there was no significant correlation between scores of E-cadherin and tumor metastasis to the lymph nodes, as the p value more than 0.05 (table 6), there was no published data that correlate E-cadherin expression score with breast cancer metastasis to the lymph nodes.

We found only one sample from male not included in this study, this sample with grade 3 IDC, his E-CD result showed negative (score 0.0) expression, these finding agree with the fact that breast cancer is rare in men with an incidence less than 1% of that encountered for women, typically diagnosed in advanced age, because of the scant amount of breast tissue in men; the tumor rapidly infiltrates the overlying skin and underlying thoracic wall, unfortunately almost half tumor spread to regional nodes or more distant sites by the tissue they are discovered.[17]

5.1 CONCLUSION

On the obtained results this study concluded that;

- The commonest age group with breast cancer in Sudan is menopause women.
- The commonest breast cancer in Sudan is IDC followed by ILC.
- Most of breast cancer cases in Sudan present with advanced grades of the tumor.
- Most of breast cancer cases in Sudan present with cancer invasion to lymph nodes.

- ❖ E-cadherin expression score decreases with progression of tumor grades.
- ❖ E-cadherin expression and its score decreases with invasion of the tumor to lymph nodes.

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