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RESEARCH ARTICLE
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Expression of Fibronectin and Matrixmetalloproteinase-1(MMP-1) In Breast Cancer Patients in Basrah Province

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ABSTRACT

Fibronectin is an extracellular matrix protein that is expressed in almost all types of cancers and plays a crucial role in tumor growth promotion, survival and resistance to therapy. Matrix metalloproteinases (MMPs) are a family of enzymes implicated in the degradation and remodeling of extracellular matrix and in vascularization. The present study involved 82 samples including 57 patients of breast cancer and 25 as control (breast benign tumor). When the ELISA levels of MMP-1 in cancer patients were compared to its levels in benign tumor patients, it was noticed that the levels in cancer patients were significantly statistically higher than the levels in benign tumor patients. No such significance could be noticed when ELISA FN was tested. The comparison, of ELISA MMP-1 and ELISA FN in cancer patients sub-grouped according to type, stage, and grade of the tumor, shows that there are differences in the measures of central location and measures of dispersion. Results showed there was no any significant statistical difference in the presence of IHC MMP-1 and the presence of IHC FN between both groups, cancer and benign tumor patients. The IHC MMP-1 presence in cancer patients was investigated according to the characteristics of the malignancy, type, stage, and grade and no conclusive results could be elicited. Also, when the IHC FN presence in cancer patients was investigated according to the characteristics of the malignancy, type, stage, and grade, again no conclusive results could be elicited.

Keywords: *Fibronectin, Matrixmetalloproteinase-1(MMP-1), Breast Cancer*

INTRODUCTION

Breast cancer is one of the most frequently diagnosed cancers and it is the leading cause of cancer death in females worldwide; comprising 23% of the total new cancer cases and 14% of the total cancer death in 2008; worldwide breast cancer is the fifth most common cause of cancer mortality (Qassim, 2015) . Some statistical studies in Iraq demonstrated that breast tumor is the commonest type of female malignancy representing around one third of the registered female tumors from the most recent Iraqi Cancer Registry, making breast cancer is the main malignancy site among the Iraqi population (Iraqi cancer Registry, 2010 ; Alwan and AL-Rufaee , 2010). In Basrah , the southern province in Iraq , breast cancer is still reported as the overlapping cancer among females (Habib, et al ,2007; Habib, et al 2016 and Abood, 2018).

The extracellular matrix (ECM) is increasingly recognized as an important regulator in breast cancer. ECM in breast cancer development showed numerous changes in composition and organization when compared to the mammary gland under homeostasis. Matrix proteins that are induced in breast cancer include fibrillar collagens, fibronectin, specific laminins and proteoglycans as well as matricellular proteins (Insua-Rodrígue and Oskarsson, 2016).

Fibronectin (FN) is a worldwide and essential component of the extracellular matrix. It functions both as a regulator of cellular processes and an important scaffolding protein to maintain and direct tissue organization and ECM composition (To and Midwood, 2011). FN, is a glycoprotein in an extracellular matrix and also a mesenchymal creator of EMT, has been involved in the development of multiple types of human cancer(Jia, et al., 2010). The FN serves as a central organizer of ECM molecules and mediates between the tumor microenvironment and cancer cells. Its upregulation is correlated with angiogenesis, cancer progression, metastasis, and drug resistance. Because of the prevalence of FN overexpression in cancer, FN targeting imaging agents and therapeutics have the promise of broad applications in the diagnosis, treatment, and image-guided interventions of many types of cancers (Han and Lu, 2017). Fibronectin also facilitates the invasion of cancer cells by changing ECM stability and by inducing the expression and secretion of certain matrix metalloproteases (MMPs) that dissolve the matrix surrounding the tumor cells and enable their entry into the vascular system. As cancer cell survival during circulation is also crucial for development of metastases, it has also been demonstrated that the fibronectin helps the tumor cells to bind to platelets protecting them from the immune system (Fernandez-Garcia, et al., 2014).

Matrix metalloproteases (MMPs) are a multigene family of zinc-dependent endopeptidases that share a similar structure and which collectively, have the capacity to degrade virtually every component of the extracellular matrix(Roy, et al., 2009). Increased MMP-1 expression has been associated with the incidence or invasiveness of various types of cancer, including colorectal, esophageal, pancreatic, gastric, breast, and malignant melanoma(Liu, et al., 2012). MMP-1 cleave EXM components and thus play an important role in tumor invasion. MMP-1 is produced by tumor cells as well as by tumor associated stroma. High expression of MMP1 in tumor is associated with tumor evolution, poor prognosis and shortened survival in different types of tumors including breast cancer (Roy et al., 2009). The MMP-1 level is also markedly upregulated in breast cancer and stromal cells, and is associated with breast cancer progression and poor prognosis (Boström, et al., 2011). Many studies suggest that overexpression of MMPs is one of the key events leading to the breast cancer dissemination. Recently, it was shown, that MMPs induce epithelial to mesenchymal transition and thus increase the invasive potential of tumor cells (Mannello , 2011).

Aim of the study

The current study, aimed to investigate the expression and clinical relevance of FN in breast cancer explore its relationship with the expression of matrix metalloproteinase-1(MMP-1), by the measuring the levels of MMP-1 and FN in serum and tissue of breast tumor by ELISA and immunohistochemistry.

MATERIALS AND METHODS

The study was approved by the medical ethics committee of Iraqi Ministry of Health and was done on 82 Iraqi patient women. Between October 2021 and August 2022 , a total of (57) women, aged 31 -75, with breast cancer and (25) women, aged 22– 49 with benign tumor. All Breast cancer patients received chemotherapy or radiotherapy or treatment with mastectomy before blood collection. The present study evaluated the expression levels of MMP-1 and FN in cancerous and non-cancerous samples in different aspects on protein levels (in tissue and serum).

Serum

Blood samples were taken from 28 patients with breast cancer and 12 women with benign tumor

allowed to clot. After centrifugation serum was stored at −20°C until required.

Enzyme-linked immunosorbent assay(ELISA)

Enzyme-linked immunosorbent assay (ELISA) for serum MMP-1 and FN was performed using commercially available ELISA kit (My Bio Source , USA). The analysis was performed according to the manufacturer's instructions. Calculation of results was achieved by the construction of standard curve.

Immunohistochemical staining

Paraffin embedded tissue blocks were obtained from the histopathology department to the same patients. Four μM section of paraffin embedded tissue, was cut by microtome and floated in water bath (40°C) containing distilled water. The sections were transferred onto charged slides suitable for immunohistochemistry, then the slides allowed to dry overnight at 37˚C (baking slide), thereafter the staining was carried out according to manufacturer's instructions provided with differential IHC –P kit . (Avwioro., 2011).

RESULTS

The results of the concentration of MMP-1 and FN that were investigated by ELIZA technique, using blood samples from breast cancer and benign tumor patients showed MMP-1 exhibited a significant difference (P=0.006) in cancer patients compared with a benign tumor, the median value of MMP-1 was (1969.50), (906.00) respectively. Whereas, FN was no such significance (p=0.056) that could be noticed when FN was tested (138.00) (69.00) respectively (Table-1). In order to investigate that, whereas MMP-1 was affected by the stages and grade the results revealed there was significant (P=0.048), (P=0.033) respectively. Whereas, results of FN according to stage and grade showed no significance (P=0.857),(p= 0.920) respectively (Table -2).

The immunohistochemistry results showed that there was no any significant statistical difference in the presence of MMP-1 in cancer and benign tumor patients (p= 0.418) and the presence of FN between both groups (p= 0.752). Figure(1).

According to the stage and grade of cancer in the present study, the results showed there was no significant difference for MMP-1 (P=0.068), (P=0.052) respectively, Table(3). According to the stage and grade of cancer in the present study, the result showed there was no significant difference for FN (P=0.781),(P=0.696) respectively, Table(4).

TABLE 1: Comparison according to the type of tumor in serum.

`Category		**Conc.MMP1**	**Conc.FN**
Cancer patient	N	28	28
	Mean± SD	2550.93±1527.370	130.93±27.594
	Median	1969.50	138.00
	Minimum	675	36
	Maximum	6500	150
Benign tumor patient	N	12	12
	Mean± SD	1196.83±978.929	84.17±55.746
	Median	906.00	69.00
	Minimum	150	25
	Maximum	2899	146
P-value*		0.006	0.056

TABLE 2: Comparison between levels of MMP1 and levels of FN in cancer patients grouped according to the stage, and grade in serum.

Marker	Parameter	Stage			P-value
		I	II	III	
Conc.MMP1	Mean±SD	1309.5±812.47	2134.08±1455.85	3158.77±1493	0.048
	Median (Min.-Max.)	1309.5 (735-1884)	1747 (675-6500)	3302 (900-5320)	
	No.	2	13	13	
Conc. FN	Mean±SD	133.5±4.95	130.77±28.71	130.69±29.76	0.857
	Median (Min.-Max.)	133.5 (130-137)	139 (40-150)	139 (36-150)	
	No.	2	13	13	
		Grade			
		1	2	3	
Conc. MMP1	Mean±SD	1309.5±812.47	2134.08±1455.85	3158.77±1493	0.033
	Median (Min.-Max.)	1309.5 (735-1884)	1747 (675-6500)	3302 (900-5320)	
	No.	2	13	13	
Conc. FN	Mean±SD	133.5±4.95	130.77±28.71	130.69±29.76	0.920
	Median (Min.-Max.)	133.5 (130-137)	139 (40-150)	139 (36-150)	
	No.	2	13	13	

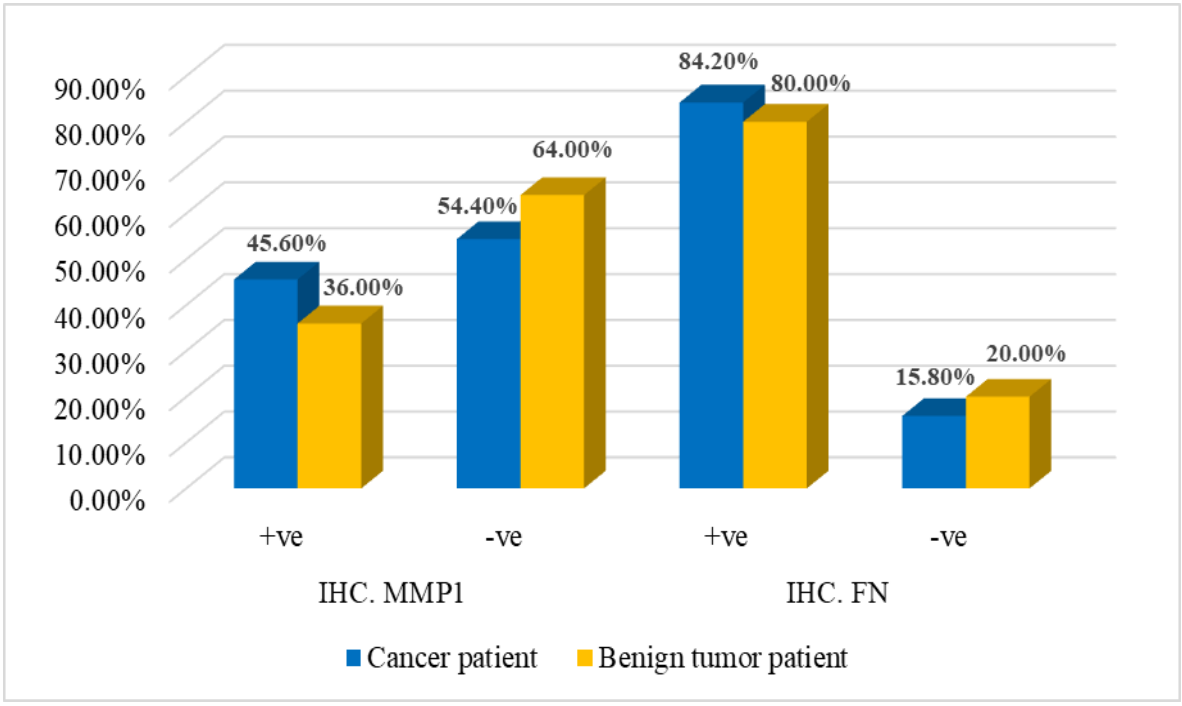

FIGURE 1: Comparison of cancer and benign tumor patients grouped according to the presence of MMP1 and FN.

TABLE 3: Distribution of the presence of MMP1 grouped according to stage and grade of cancer in tissue.

Characteristic	IHC. MMP1		Total	P-value
	+ve	-ve		
Stage:				
I	0	2	2	
	0.0%	100.0%	100.0%	
II	18	13	31	0.068
	58.0%	41.9%	100.0%	
III	8	16	24	
	33.3%	66.7%	100.0%	
Grade:				
G1	0	2	2	
	0.0%	100.0%	100.0%	
G2	20	15	35	0.052
	57.1%	42.9%	100.0%	
G3	6	14	20	
	30.0%	70.0%	100.0%	
Total	26	31	57	
	45.6%	54.4%	100.0%	

TABLE 4: Distribution of the presence of FN grouped according to stage , and grade of cancer in tissue.

Characteristic	IHC. FN		Total	P-value
	+ve	-ve		
Stage:				
I	1	1	2	
	50.0%	50.0%	100.0%	
II	27	4	31	0.781
	87.1%	12.9%	100.0%	
III	20	4	24	
	83.3%	16.7%	100.0%	
Total	48	9	57	
	84.2%	15.8%	100.0%	
Grade:				
G1	1	1	2	
	50.0%	50.0%	100.0%	
G2	29	6	35	0.696
	82.9%	17.1%	100.0%	
G3	18	2	20	
	90.0%	10.0%	100.0%	
Total	48	9	57	
	84.2%	15.8%	100.0%	

Figure (2), showed the FN expression levels were determined by immunohistochemistry, since the revealing a strong homogenous staining of cancer cells in the samples that analyzed. Detection of FN breast carcinoma section showed extensive FN production in the surrounding stroma, Sections from malignant breast tumor showing the positive staining as moderate, and strong. Figure (4) showed the study of MMP-1 confirmed that the enzyme

expressed in the cytoplasm which appeared as brown granules. A proportion of positive cells are visualized in the field represented expression as high positive stain , while other showed negative stain.

On the other hand other sections have been taken from benign tumor showed the FN and MMP-1 very weak, moderate, and strong expression, while one of them showed negative stain, Figure (3) and Figure (5).

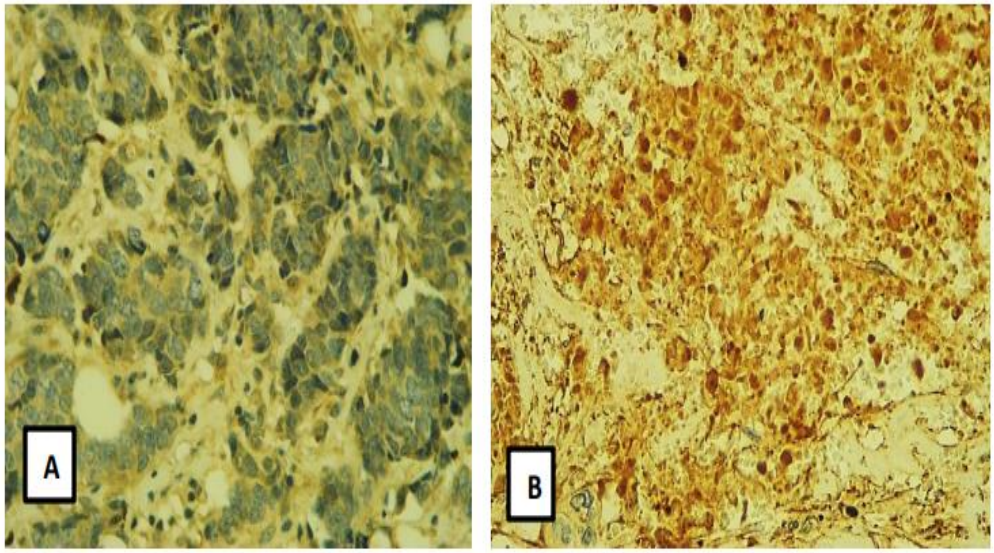

FIGURE 2: Immunohistochemistry (IHC) analysis showing the FN expression in the extracellular matrix appear as brown granules . A, immunohistochemical detection of FN in human Breast Cancer which show moderate positive (arrow). B, immunohistochemical detection of FN in human Breast Cancer which show strong positive (arrow) (400X).

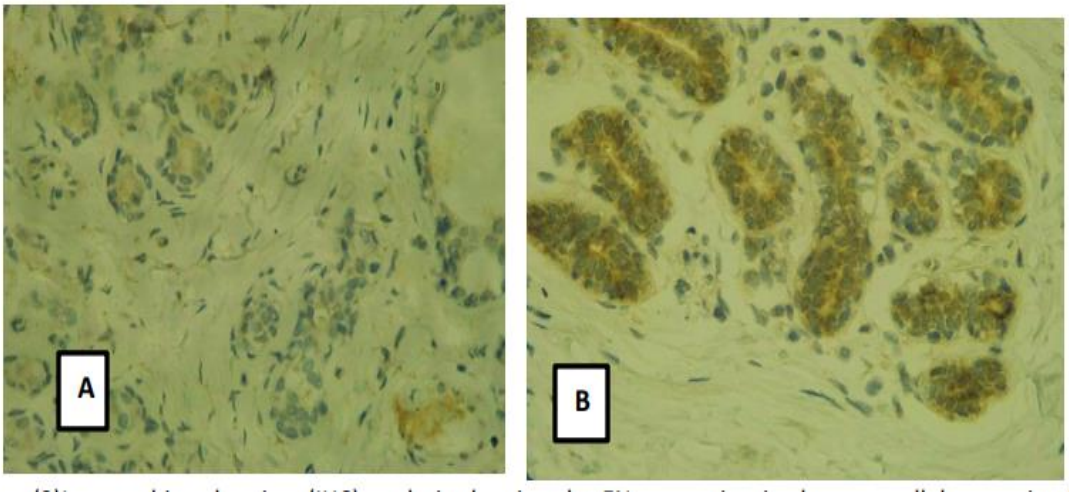

FIGURE 3: Immunohistochemistry(IHC) analysis showing the FN expression in the extracellular matrix of breast benign tumor appear as, , A, immunohistochemical detection of FN which show brown granules, weak positive (arrow) (400X).,B, immunohistochemical detection of FN which show moderate positive (400X).

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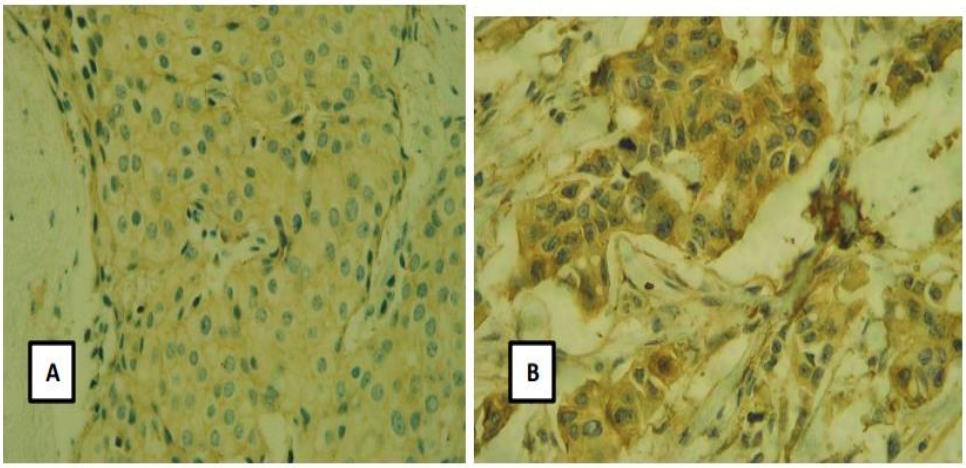

FIGURE 4: Immunohistochemistry (IHC) analysis showing the MMP-1 expression in the cytoplasm appear as , A, immunohistochemical detection of MMP-1 in human Breast cancer which show negative score (400X). B, immunohistochemical detection of FN in human Breast cancer which show strong positive (arrow) (400X).

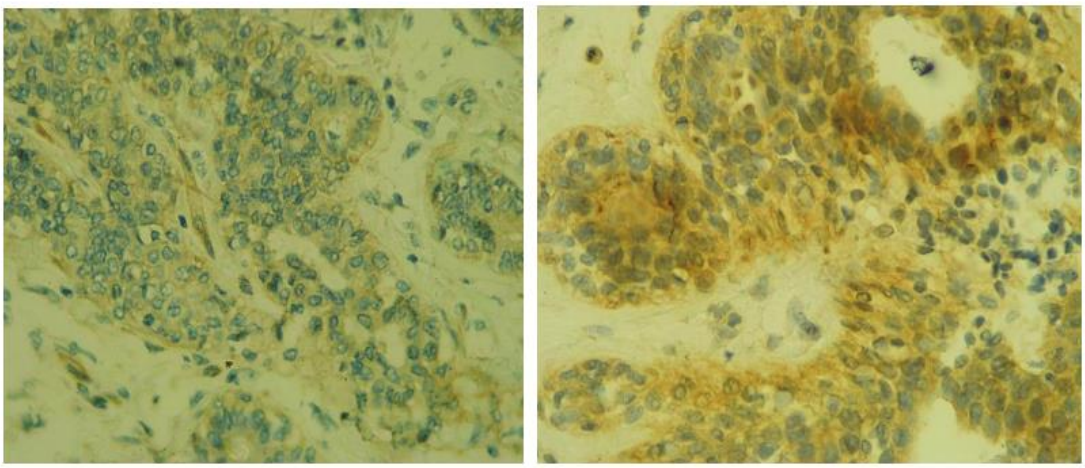

FIGURE 5: Immunohistochemistry (IHC) analysis showing the MMP-1 expression in the cytoplasm of breast benign tumor appear as,). A, immunohistochemical detection of MMP-1 which show brown granules weak positive (arrow) (400X). B, immunohistochemical detection of MMP-1 which show brown granules strong positive (arrow) (400X).

DISCUSSION

The FN is an important component of the extracellular matrix and serves a role in the pathogenesis of multiple malignancies. The expression of FN also affects the outcome for patients with cancer (Tas, et al., 2016). As well the result was no significant between FN in both tumor size and histological grade, these results agreement with other study by Moon, et al. (2016). The present study demonstrated that FN concentration in serum were significantly higher in both patients with breast cancer in the test set and in benign. Kenny, et al., (2014) reported that function and expression of FN in cancer cells has been found to be expressed in breast cancer and other cancers . Moreover, other study has been reported that FN could induce progression of various cancer cells and is strongly expressed in breast carcinoma, and its distribution is different from that of normal breast parenchyma (Li, et al., 2015).

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The results showed that the levels of MMP-1 in serum were significantly higher in breast cancer patients than in control group, this result was similar with a study carried by Jarrah , (2019) who showed a statistically significant difference in MMP(2-9) levels between the breast cancer and benign breast tumor patient groups. The present study showed overexpression of MMP-1 in serum of malignant tumor in Basrah women comparison to breast benign tumor may be due to MMPs in normal tissue found as an inactive form but been active in cancer cells. According to the result, the stage and grade of breast cancer showed an association with the expression of MMP-1, and this was agreement with other studies that showed, MMP-1 expression was also significantly increased in aggressive breast tumors and correlates with both tumor size and histological grade (McGowan and Duffy, 2008).Other studies showed no association between given parameters and expression of MMP-1 (Argote Camacho, et al., 2021; Wang, et al., 2019). On the other hand, the mean serum MMP-1 level was found to be decreased in the breast cancer group, in an inverse association with tumor size (Decock, et al., 2008).

The present study showed there was no any significant statistical difference in the presence of IHC MMP-1 and the presence of IHC FN between both groups, cancer and benign tumor patients.

Breast cancer metastasis is closely associated with the changes in the surrounding carcinomatous interstitium, and aberrant MMP-1 expression affects this, making it a potential biomarker. affects this, making it a potential biomarker.

None of the stage or the grade of breast cancer showed an association with the expression of MMP-1, and this was agreement with other studies that showed no association between given parameters and expression of MMP-1 (Ma, et al., 2018; Argote Camacho , et al., 2021; Wang, et al., 2017; Mohammed, 2021).

In Immunohistochemistry analysis, we identified that MMP-1 protein expression was high in breast cancerous tissues than corresponding normal tissues. We also analyzed the relationship between MMP-1 protein expression, tumor size, , differential grade. MMP-1 has been revealed to be expression in breast cancer confirmation of this and a better understanding of MMP-1 overexpression in breast cancer may provide a novel insight into the role of MMP-1 in breast cancer pathogenesis and progression (Gialeli, et al., 2011).

In the current study, the immunohistochemistry of studied sample showed that higher expression of FN for both malignant and benign tumor. FN was positive in more than 84% samples with malignant tumor. These results not associated with clinicopathological parameters stage, grade, and hormone receptors .This was confirmed by one of the studies, no significant correlation was observed for histological grading, TNM group stage, lymph node metastasis and the presence of distant metastases (Waalkes, et al., 2010). While Bae , et al.,(2013) revealed that expression of FN was significant correlation with clinicopathologic parameters representing, poor prognosis, high histologic grade, lymphovascular invasion, hormone receptor, and HER2. On the other hand current data indicates that malignant cells has spread, it is associated with a poor survival and a higher risk of resistance to systemic therapy .

CONCLUSION

The present study concludes the following:

1. Increased of FN in both serum and tissue of benign and malignant breast tumor.
2. Increased of MMP-1 in serum of malignant breast tumor than in benign tumor.
3. Highly expression of MMP-1 in serum with the development of disease.
4. Highly expression of FN in tissue with the development of disease.

RECOMMENDATIONS

1. Study the molecular and gene expression are needed for FN and MMPs associated with cancer overexpression.
2. Use of MMP-1 and FN as biomarkers for the diagnosis of breast cancer stage , grades and metastasis.
3. Study Fibronectin types (Pfn and cFN) and its role in cancer disease.

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4. Additional studies of other types of MMPs and their association with FN in cancer.

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