

Possible etiological role of Ezrin and Moesin in progression of breast cancer in Iraqi woman

Posible papel etiológico de Ezrin y Moesin en la progresión del cáncer de mama en la mujer iraquí

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Abstract

Background: Breast cancer (BC) is the most common malignancy in women and the second greatest cause of cancer death in Iraq (BC) reported the first type of cancer.

Methods: A case-control study was conducted to assess the role of Moesin and Ezrin in pathogenicity of breast cancer in Iraqi women. The study included 50 patients with BC age matched with 50 healthy individuals served as a control group. The Moesin and Ezrin concentrations were determined by enzyme-linked immunosorbent assay (ELISA) technique.

Results: The result showed that there was a significant increasing in Ezrin and Moesin serum level in Patients Versus control and there was significant difference in both adherent molecule serum as related with age group of the two under studied groups. But there is no significant difference between serum level of (EZ andMO) with grade and stage of disease.

Conclusion: According to the current result, Ezrin and Moesin may has a role in the aggressiveness of diseases, so it may consider a good therapeutic target to reduce the aggressiveness of disease.

Key words: Breast cancer, Moesin, Ezrin, metastasis.

Resumen

Antecedentes: El cáncer de mama (CB) es la neoplasia maligna más frecuente en las mujeres y la segunda causa de muerte por cáncer en Irak.

Métodos: Se realizó un estudio de casos y controles para evaluar el papel de Moesin y Ezrin en la patogenicidad del cáncer de mama en mujeres iraquíes. El estudio incluyó a 50 pacientes con CB emparejados por edad con 50 individuos sanos que sirvieron de grupo de control. Las concentraciones de Moesin y Ezrin se determinaron mediante la técnica de ensayo inmunoenzimático (ELISA).

Resultados: Los resultados mostraron que hubo un aumento significativo del nivel sérico de Ezrin y Moesin en los pacientes frente al grupo de control y hubo una diferencia significativa en el suero de ambas moléculas adheridas en relación con el grupo de edad de los dos grupos estudiados. Sin embargo, no hay diferencias significativas entre el nivel sérico de (EZ andMO) con el grado y el estadio de la enfermedad.

Conclusión: De acuerdo con los resultados actuales, la Ezrina y la Moesina pueden desempeñar un papel en la agresividad de las enfermedades, por lo que pueden considerarse una buena diana terapéutica para reducir la agresividad de la enfermedad.

Palabras clave: Cáncer de mama, Moesin, Ezrin, metástasis.

Introduction

Cancer is widely known as a silent killer and continues to list as one of the leading causes of death worldwide, claiming millions of lives every year. It is quite common around the world, in both developing and developed countries. Despite the dangers associated with cancer, awareness is yet poor in our society. Prevention and mitigation of risk factors are the best way of combating cancer, and poor awareness could delay the process¹. Breast cancer (BC) is defined as a malignant tumor that arises from the breast's ducts or lobules². It is the most often diagnosed cancer in women, accounting for 11.6% of newly diagnosed cancer cases and 6.6% of estimated cancer mortality worldwide between 2006 and 2012, the incidence of breast cancer in Iraq increased significantly, rising from 30 per 100000 to 40 per 100000. In 2011, there were 3763 cases of breast cancer in Iraq, with an incidence rate of around 23.01 per 100000 females, compared to 16.65 per 100000 females in 2008⁴. In Iraq, breast cancer was the most frequent malignancy, with 4529 cases reported in 2013, with 4422 females and 107 males, a proportion of the total of 18.84% and a rate of 12.9 per 100.000 people. As a result, breast cancer is the first of the top ten malignant neoplasms affecting the community⁵⁻⁶. In 2016, 897 women died as a result of this disease, which is the leading cause of cancer-related mortality among Iraqi females 23.6% and the second overall 12.1% among males and females after bronchogenic carcinoma¹⁻³. The main characteristic of tumor cells is their disrupted adhesion to the ECM, which results in the loss of control over normal cell function. This attachment is important for signal transduction from the outside to the inside of the cell, which stimulates many activities such as cell cycle progression, and cells that separate from the ECM die via apoptosis⁴⁻⁵.

Metastasis of malignant tumors are the cause of over 90% of cancer related deaths. The primary tumor cells attack the local environment and infiltrate blood or lymphatic vessels walls in order to produce a metastatic lesion, to survive in the circulatory system, and invade to the distant organ⁷.

Cell adhesion molecules are glycoproteins expressed on the cell surface and play an important role in inflammatory as well as neoplastic diseases. There are four main groups: the integrin family, the immunoglobulin superfamily selectins, and cadherins⁸⁻⁹. Moesin is an Ezrin-radixin-Moesin (ERM) family protein and connects the actin cytoskeleton to transmembrane receptors. It belongs to the band 4.1 superfamily, which share a 300-amino-acid domain termed the 4.1 ERM domain. ERM members serve an important role in regulating cell adhesion, migration and morphogenesis, by regulating actin cytoskeleton remodeling. Ezrin, which is known as a cytoskeleton linker protein, is closely linked with the metastatic progression of cancer and is frequently abnormally expressed in aggressive cancer types.

However, the possible involvement of Ezrin in metastasis and angiogenesis in breast cancer remains unclear. Ezrin, an important member of the Ezrin-radixin-Moesin (ERM) family of cytoskeleton-associated proteins, is a transit protein between membrane proteins and actin filaments.

Materials and methods

Subject: Baghdad, Iraq's capital, receives thousands of visitors each day. The medical city's oncology teaching hospital in Baghdad is one of Iraq's largest centers, employing thousands of Iraqis from all around the country. As a result, the participants in the study may be representative of the Iraqi population. From November 2021 to January 2022, a case-control study was done in the biology department, college of education, university of Baghdad. This study involved 100 women who were separated into two groups: breast cancer woman (n=50) as patients group and apparently healthy women (n=50) who served as controls. Women diagnosed with breast cancer by specialist physicians. Mammography or histological findings confirmed the diagnosis of breast cancer. The study excluded cases that had other forms of cancer or were treated with mastectomy, chemotherapy, or radio therapy. A healthy control group was enrolled that did not have breast cancer, other types of cancer, or any history of acute or chronic disease (T2DM, liver disease, or autoimmune disease). Questionnaires were used to ask all participants in the current study about their age, family history, medical history, and other diseases. The ethical committee at Baghdad University accepted the study procedure, and all participants completed a written informed consent document. Blood samples: In a plain tube, all individuals' peripheral blood samples were collected. By using an enzyme linked immunosorbent assay (ELISA), adhesion molecules markers such as Human Moesin (MSN) and Human cytovillin /Ezrin ELISA were measured. The concentrations of circulating Moesin and Ezrin in plasma were determined using a commercial ELISA kit (My Bio source) according to the manufacturer's instructions (Cat .No: MBS076337 and Cat.No:MBS162342 respectively).

Statistical analysis

Statistically, all data were analysis SPSS program (IBM V .28); Independent T test and one way ANOVA test were used to measure P value using least significant differences (LSD). All data were presented as mean \pm S.E., and p value <0.05 was considered as significant differences.

Results

Ezrin serum level

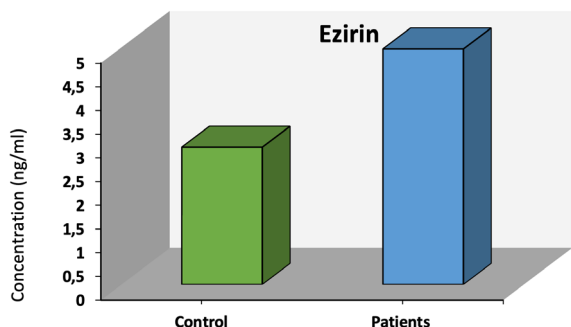
As show in **table I** and **figure 1** which demonstrate the serum level of Ezrin in patients and control, the

result represented by (mean± SE), the result for Ezrin serum level in patient and control was (2.895±0.178, 4.967±0.128) Pg/ml respectively P value was (<0.001) the result showed a high significant increase in patient compared to control.

Table I: Serum level of Ezrin in patients and control.

Group	Ezrin (Mean±S.E.)	P value
Control (N=40)	2.895±0.178	<0.001**
Patients (N=50)	4.967±0.128	

Figure 1: Serum level of Ezrin in patients and control.



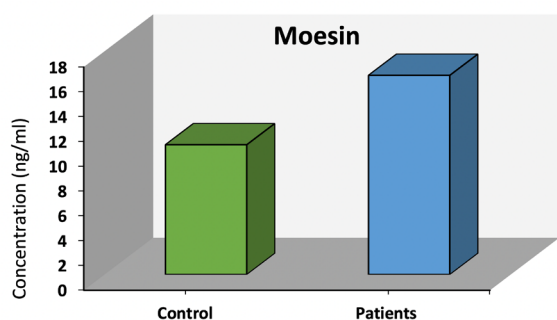
Moesin serum level

In **table II** and **figure 2** we observed a high significant increase in serum level of Moesin in patient as compared to control P<0.001.the result for Moesin serum level in patient and control was (10.463±0.554, 16.061±0.281) PG/ml respectively .

Table II: Serum level of Moesin in patient and control.

Group	Moesin (Mean±S.E.)	P value
Control (N=40)	10.463±0.554	<0.001**
Patients (N=50)	16.061±0.281	

Figure 2: Serum level of Moesin in patient and control.



Ezrin serum level distribution according to age groups

As shown in **table III** which demonstrated the distribution of Ezrin serum level according to the age group. Ezrin serum level for age groups (30-40/41-50/51-65) Years was (3.097±0.254, 4.724±0.369/2.824±0.464, 5.11±0.171/2.734±0.25, 4.968±0.194) pg/ml

respectively. There was a non-significant difference among the age group patient p (0.537). Also there was no significant difference among control age groups p (0.678) while there was a significant difference between patients and control in each age group.

Table III: Ezrin serum level distribution according to age groups in patients and control.

Age Group (yrs.)	Control	Patients	P value
	(Mean±S.E.)		
30-40	3.097±0.254	4.724±0.369	<0.001
41-50	2.824±0.464	5.11±0.171	<0.001
51-65	2.734±0.25	4.968±0.194	<0.001
P value	0.678	0.537	-

Moesin serum level distribution according to age group

As shown in **table IV** which demonstrated the distribution of Moesin serum level according to the age group. Moesin serum level for age groups (30-40/41-50/51-65) Years was (10.833±0.946, 10.027±0.989, 10.408±0.992, 15.847±0.615, 16.098±0.468, 16.125±0.442) pg/ml respectively. There was a non-significant difference among the age group patient p (0.932). Also there was no significant difference among control age groups p(0.85) while there was a significant difference between patients and control in each age group.

Table IV: Moesin serum level distribution according to age groups in patients and control.

Age Group (yrs.)	Control	Patients	P value
	(Mean±S.E.)		
30-40	10.833±0.946	15.847±0.615	<0.001
41-50	10.027±0.989	16.098±0.468	<0.001
51-65	10.408±0.992	16.125±0.442	<0.001
P value	0.85	0.932	-

Ezrin serum level according to grade in patients

The result as shown in **table V** Ezrin serum level in patients according to grade of disease which were (grade I, II, III) was (4.868±0.266, 4.876±0.136, 5.387±0.385) PG/ml respectively ,There was no significant differences among the grade of disease p value (0.991, 0.465, 0.991, 0.132, 0.132, 0.132) for each grade respectively.

Table V: Ezrin serum level according to grade in patients.

Grade	Ezrin (Mean±S.E.)	P value		
		Grade I	Grade II	Grade III
Grade I (n=2)	4.868±0.266	-	0.991	0.132
Grade II (n=39)	4.876±0.136	0.991	-	0.132
Grade III (n=9)	5.387±0.385	0.465	0.132	-

Moesin serum level according to grade in patients

In **table VI** which clarify Moesin serum level in patients according to grade of disease which were (grade I, II, III) the result was (17.246±4.175, 15.811±0.29, 16.879±0.562) PG/ml respectively ,There was no significant differences among the stages of disease p

value (0.319, 0.812, 0.319, 0.15, 0.812, 0.15) for each grade respectively .

Table VI: Moesin serum level according to grade in patients.

Grade	Ezrin (Mean±S.E.)	P value		
		Grade I	Grade II	Grade III
Grade I (n=2)	17.246±4.175	-	0.319	0.812
Grade II (n=39)	15.811±0.29	0.319	-	0.15
Grade III (n=9)	16.879±0.562	0.812	0.15	-

Ezrin serum level in related to stage in patients

As shown in **table VII** which explain Ezrin serum level in patients according to stage of disease which were (stage IA, IIA, IIB, IIIA, IIIC, 4) The result was (5.015±0.432, 4.82±0.203, 5.363±0.317, 5.078±0.297, 4.351±0.372, 5.124±0.369) PG/ml respectively ,There was no significant differences among the stages of disease except in stage IIB and IIC there was a significant decrease Ezrin serum level p (0.035, 0.035).

Table VII: Ezrin serum level in related to stage in patients.

Stage	Ezrin (Mean±S.E.)	P value					
		Stage IA	Stage IIA	Stage IIB	Stage IIIA	Stage IIIC	Stage 4
Stage IA (n=4)	5.015±0.432	-	0.701	0.515	0.914	0.259	0.843
Stage IIA (n=16)	4.82±0.203	0.701	-	0.141	0.552	0.281	0.439
Stage IIB (n=10)	5.363±0.317	0.515	0.141	-	0.541	0.035	0.577
Stage IIIA (n=6)	5.078±0.297	0.914	0.552	0.541	-	0.168	0.925
Stage IIIC (n=8)	4.351±0.372	0.259	0.281	0.035	0.168	-	0.118
Stage 4 (n=2)	5.124±0.369	0.843	0.439	0.577	0.925	0.118	-

Moesin serum level according to stage in patients

As shown in **table VIII** which illustrated Moesin serum level in patients according to stages of disease (stage IA, IIA, IIB, IIIA, IIIC,4) the result was(15.822±1.639, 15.745±0.558, 16.252±0.558, 16.127±0.390, 16.031±0.946, 16.545±0.632) PG/ml respectively. There was no significant differences among the stages of disease.

Table VIII: Moesin serum level according to stage in patients.

Stage	Moesin (Mean±S.E.)	P value					
		Stage IA	Stage IIA	Stage IIB	Stage IIIA	Stage IIIC	Stage 4
Stage IA (n=4)	15.822±1.639	-	0.947	0.727	0.82	0.876	0.572
Stage IIA (n=16)	15.745±0.558	0.947	-	0.547	0.702	0.774	0.377
Stage IIB (n=10)	16.252±0.558	0.727	0.547	-	0.908	0.838	0.767
Stage IIIA (n=6)	16.127±0.390	0.82	0.702	0.908	-	0.937	0.711
Stage IIIC (n=8)	16.031±0.946	0.876	0.774	0.838	0.937	-	0.649
Stage 4 (n=2)	16.545±0.632	0.572	0.377	0.767	0.711	0.649	-

Correlation between Ezrin and Moesin related to age

According to the correlation result, we observed that There was a moderate significant correlation between age and Ezrin, and no correlation between age and Moesin, however according to the findings there was a high significant correlation between Ezrin and Moesin.

Table IX: Correlation between Ezrin and Moesin related to age.

	Parameter	Ezrin	Moesin
Age	Pearson Correlation Sig. (2-tailed)	0.203* 0.05	0.201 0.057
Ezrin	Pearson Correlation Sig. (2-tailed)	- -	0.776** <0.001
Moesin	Pearson Correlation Sig. (2-tailed)	0.776** <0.001	- -

Correlation between Ezrin and Moesin related to grade and stage

According to the findings There was no correlation with stage and the two adherent molecules Ezrin and Moesin, The result for stage was (-0.135, 0.352, -0.063, 0.662) and no correlation between grade and the two adherent molecules Ezrin and Moesin. The result for grade was (0.198, 0.167, 0.113, 0.433).

Table X: Correlation between Ezrin and Moesin related to grade and stage.

	Parameter	Grade	Stage
Ezrin	Pearson Correlation Sig. (2-tailed)	0.198 0.167	-0.135 0.352
Moesin	Pearson Correlation Sig. (2-tailed)	0.113 0.433	-0.063 0.662

Discussion

Previous studies have confirmed that metastasis is a complex process involving. A series of changes, such as mesenchymal transition of local cancer cell, reorganization of actin cytoskeleton, remodeling of the micro-environment and colonization of metastatic cell, plasminogen, fibronectin, Moesin, Ezrin, an important member.

Ezrin. radixin-Moesin (ERM) Family Cytoskeleton associated protein, is a transit protein between membrane Protein and actin filament, never the less emerging evidence has demonstrated that Ezrin may serve as metastasis-related oncogene through modulating multiple cellular process, including the formation of Microvilli maintenance of cellular morphology and intracellular connection and promotion of cellular motility and invasion.

To determine the potential function of Ezrin adherent molecule in the pathogenesis of BC, we first assessed the Ezrin serum level by ELISA techniques. and the result found that there was a significant elevation in Ezrin serum level in patients versus control as shown in **table I**.

This result was Correspond with study performed by¹⁰ which recorded an up regulation in Ezrin expression in BC and correlated with poor outcome and they suggest that Ezrin may function as oncogene while¹¹ observed a down regulation in intra hepatic cholangiocarcinoma and its loss was shown to result a more aggressive phenotype, so this data indicated that Ezrin may also serve as a tumor Suppressor.

The investigation done by¹² who studied Ezrin expression in breast carcinoma using tissue micro array, in most breast cancer (70.3%) the Ezrin staining in normal breast epithelium localized in the cytoplasm and there was a significant positive association between cytoplasmic and adverse tumor properties such a high grade, hormonal receptor negativity and Lymph node metastasis, so they suggest that the Change of Ezrin localization from apical membrane to the cytoplasm is correlated with adverse feature in invasive breast tumor. In spite of the difference between our study and David's study, but we share the same result which indicated this indicate to the increasing expression of Ezrin rather than their switch Localization.

In related to age group which demonstrated in **table III** the result showed that there was a significant difference between each age group for patient versus control $p < 0.001$, while there is no significant difference among each group $p(0.678, 0.537)$ respectively this indicate that age has an impact on disease but with no association with the disease duration time.

In regard to grade, our result indicated that there is no association between Ezrin serum level as described in **table V** and grade (I, II and III). this result did not consistent with result recorded by¹³⁻¹⁴.

Also ¹⁵ which indicated that the over expression of Ezrin affect the process of hepatocellular Carcinoma cell proliferation and migration and invasion found that Ezrin was upregulated in BC disease which was linked with aggressive tumor characteristic and poor prognosis more over they showed that Ezrin promote BC proliferation, migration, invasion and angiogenesis in vitro and in vivo and this can be mediated by interact Ezrin with AKT, and promoted its kinase activity ,there by regulation the AKT pathway in BC and there was a decreased Ezrin serum Level was found in these two progressed Stage about the stage of BC (IA, IIA, IIB, IIIA, IIIC, Stage 4) as Shown in **table VII**.

The statistical result showed a nonsignificant association between Ezrin serum level and each stage, except the Ezrin serum Level in stage IIB and stage IIIC, we observed a significant decrease in Ezrin serum level.

Also This finding is disagree with previous studies¹⁶ it's Kinase activity, there by regulating the AKT Pathway in BC and there was a decreased Ezrin serum Level was found in these two progressed Stage About the stage of BC (IA, IA, 1B, IIIA, stage 4).

The statistical result showed a nonsignificant association between Ezrin serum level and each stage, except the Ezrin serum Level in stage IB significant difference. stage IIIC, observed is disagree with previous studies.

Also This finding¹⁷ which indicated that Expression of Ezrin correlate with malignant Phenotype and Ezrin knockdown reverses the aggressive biological behavior of lung cancer cell.

The discrepancy between the present result and Previous studies may return to the small sample size and to the type of Samples.

Moesin is a member of Ezrin radxin Moesin family as mentioned above ,It has been demonstrated to be a prognostic significance in tumor progression, due to its role in the metastatic process, however its role in breast cancer is not well under stood.

The current result clarified that Moesin has a significant increase in patients versus to control .as mention in **table II** this result was correspond with previous study's¹⁸, which recorded a significant increasing in BC (tissue) by using IHC technique and more high than fibroadenoma notably over expression of Moesin was significantly associate with poor prognosis in patient with ER-positive breast cancer but in this point our result didn'tagree with this study because the current result demonstrated that therewas no association between Moesin serum level andthe pathological characteristic (grade andstage) as shown in **table VI** and **VIII** and the explain for this difference may related to the sample type and sample size.

Also the result showed a nonsignificant correlation between disease and age as mentioned in **table IV** which illustrated that there was a significant difference between age group of patient versus control $p < 0.001$ while there was no significantly among age group for each one (patient andcontrol) $p = 0.678, 0.537$ respectively. The significance difference between age group of patients versus control may indicated that age has an impact on disease. There is no previous studies that correlate age with Moesin serum level.

Conclusion

According to the current result, Ezrin and Moesin may has a role in the aggressiveness of diseases, so it may consider a good therapeutic target to reduce the aggressiveness of disease.

Abbreviation list

BC: Breast cancer
 ELISA :Enzyme linked immunosorbent assay
 ERM: Ezrin –radixin- Moesin
 ANOVA: Analysis of variance
 ECM: Intracellular matrix
 AKT: protein kinase B
 SPSS : Statistical package for social sciences

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: Fieldwork was done by Mariam Qassim Al-Dulemey And Haizma Mossa Alabassi. Mariam Qassim Al-dulemey performed statistical analysis. Hazima Mossa Alabassi supervised the study and Mariam Qassim Al-dulemey drafted the manuscript under his supervision. The final manuscript was read and accepted by all authors.

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