

## Determination of Integrin $\alpha$ 2 (ITGA2), Progesterone, Prolactin, Estradiol, Zinc and Vitamin C in Serum of Female Iraqi Patients with Breast Cancer

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### Abstract

Cancer is the second leading cause of death throughout the world. Breast cancer, is one of the leading mortality reasons in women from Western Countries, in Iraq, breast cancer is the second reason of death after cardiovascular Diseases.

The study was carried out of period from October/2016-january /2017 and included (90) serum samples for Iraqi women suffered from breast cancer. Samples were divided into two groups, the first group included (66) patients (females) their age rang (22-55) years which attended to (tumor unit) at medical city educational oncology hospital and Al-Amal Al-Waatanii hospital in Baghdad, the second group included (38) for females apparently healthy their age (22-55) were studied as a control group. All patients women which included in this study were enrolled to a diagnostic criteria which made according to clinical, mamografical, histological finding. All of them were early diagnosed (without treatment). The disease was diagnosed by consultant medical staff at the hospital. Three (3ml) of peripheral blood has been drawn from both understudying groups, serum isolated and placed in Eppendorf tube in deep freeze (-20) until used. To determin the understudying hormones (progesterone, prolactin and estradiol), Eliza technique has been used while vitamin c and zinc were determined sepctrophotometricly.

By ELISA technique (ITGA2) recorded a non-significant differences in patients. Progesterone recorded a significantly increasing in patients ( $P < 0.01$ ). Prolactin showed a higher significantly increasing in patients ( $p < 0.01$ ), while estradiol serum level recorded a higher significantly decreasing ( $P < 0.01$ ) in patients. The result of biochemistry study part which included zinc and vitamin C, zinc recorded a highest significantly decreasing ( $P < 0.01$ ) in patients, as well as vitamin C recorded a significantly decreasing ( $P < 0.05$ ) in patients.

According to the significant correlation between the three studied factors (integrin, progesterone and vitamin c) we may conclude that increasing level of progesterone and decreasing level of vitamin c may effect integrin expression in a downregulation manner and perhaps breast cancer occurring and prognosis.

**Keywords:** breast cancer, integrin $\alpha$ 2, progesterone, prolactin, Estradiol, zinc vitamin C.

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## 1. Introduction

Cancer is the second leading cause of death throughout the world. Breast cancer is one of the leading mortality reasons in women from Western Countries. In Iraq, breast cancer is the second reason of death after cardiovascular Diseases [1]. Breast cancer is a type of cancer producing from breast tissue, usually from the inner lining of milk ducts, or lobules that must provide the ducts with milk [2]. there were (3763) cases of breast cancer with incidence rate about (23.01) per 100,000 female population in 2011, compared to (16.65) per 100,00 Female populations in 2008 in Iraq [1]. Integrin  $\alpha 2\beta 1$  is play an important role in cancer migration and invasion. In recent study it has been observed that  $\alpha 2\beta 1$  integrins is organize cancer metastasis either via enhancing or inhibiting the dissemination process of cancer cells. Integrin  $\alpha 2\beta 1$  functions as a Collagen receptor on platelets and fibroblastes and as both a collagen and laminin receptor on endothelial cells and most epithelial cell typs [3, 4]. The previous study revealed that the progesterone receptor PR may enhance breast cancer in women [5, 6]. Prolactin (PRL) stimulate proliferation of breast cancer cells proposed that the increasing in the growth of mammary carcinomas [7, 8]. Estradiol concentration in the serum was obviously lower in breast cancer patient. Early diagnosis for breast cancer patients is important to progress outcome, and a biomarker that can detect the disease at early stage. High concentrations of zinc (Zn) have been noted in breast cancer tissue for over a decade [9]. The causative alters in Zn metabolism at the molecular level have stayed elusive [10]. There is no high-quality evidence to suppose that a vitamin C supplementation in cancer patients either enhances the antitumor impacts of chemotherapy or decreases its toxicity [11]. The study aimed to:

1. To shied light on integrin  $\alpha 2$  which may represent a therapeutic target against metastasis.
2. Serological estimation of certain hormones (prolactin, progesterone, Estradiol vitamin c and Zinc to illustrate whether these factors have a relationship with ITGA2 level and with breast cancer risk.

## 2. Material and Method

### 2.1. Samples collection

The study was carried out at the period from October/2016 to january /2017 and included (90) serum samples for Iraqi women suffered from breast cancer. Samples were divided into two groups, the first group included (66) patients (females) their age rang (22-55) years which attended to (tumor unit) at medical city educational oncology hospital and Al-amal Al-waatnii hospital in Baghdad, the second group included (38) for females apparently healthy their age (22-55) were studied as a control group. All patients women which included in this study were enrolled to a diagnostic criteria which made according to clinical, mamografical, histological finding. All of them were early diagnosed (without treatment). The disease was diagnosed by consultant medical staff at the hospital. Three (3ml) of peripheral blood has been drawn from both understudying groups, serum isolated and placed in Eppendorf tube in deep freez (-20) until used. To determine the understudying hormones (progesterone, prolactin and estradiol), Eliza technique has been used while vitamin c and zinc were determined sepectrophotometricly .

### 2.2. Carried out by using Eliza kite

Human Integrin Alpha-2 was purchased from CUSABIO, CHINA stored at -4°C Progesterone ng/ml was purchased from Accubind , USA stored at -4°C Prolactin ng/ml

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was purchased from human , Germany stored -4°C was purchased from bioactive, Germany stored at -4°C Estradiol pg/mL

stored at -4°C itaonline, Italy, zinc µg/dl was purchased from Ascorbic acid assay was purchased from Szakits ,USA stored at -4°C

### 2.3. Statistical Analysis

In order to analyze the result, the Statistical Analysis System- SAS (2012) program was used to study the effect of different factor in study parameters. Type of statistical including LSD test, t test was used to significant compare between means in this study. Estimate of correlation coefficient between difference variables SAS [12].

## 3. Results and discussion

### 3.1. Serological and Biochemistry study

#### 3.1.1. Integrin alpha 2 (ITGA2 ng/ml) level in serum

In present study as shown in Table .1 the result of integrin alpha -2 level serum showed a non-significant increasing in patients group ( $25.17 \pm 1.15$ ) compared to control ( $24.20 \pm 2.03$ ). by using a statistical testing (T test).

**Table (1):** Serum level of ITGA2 ng/ml in patients and control

The group	No.	Mean $\pm$ SE of ITGA2
Patients	64	$25.17 \pm 1.15$
Control	24	$24.20 \pm 2.03$
t-Test	---	4.686 NS
P-value	---	0.6798

NS: Non-Significant.

Integrin is formation of non-covalent, heterodimeric complexes of an  $\alpha$  and  $\beta$  subunit [13].  $\alpha 2\beta 1$  integrin functions as a Collagen receptor on platelets and fibroblasts and as both a collagen and laminin receptor on endothelial cells and most epithelial cells kinds [3, 4]. The integrin alpha 2 beta 1 play an important role in cell migration ,cell invasion in to collagen and integrin have also important role in signal transduction ,integrin alpha 2 beta 1 has addition Capacity of boosting cell proliferation depending on the kind and physical state of collagenous Matrix [14]. Although there were a lot of study which asses the concentration of integrin alpha 2 (ITGA2) as protein in tissues but this is the first time which asses its concentration in human serum (locally in Iraq and universally) .The present study revealed that there was a non-significant difference in level serum of ITGA2 in patient as compared to control as shown in (Table1),the result was disagree Ding *et al* [15] who recorded that the lower ITGA2 protein level was recorded in breast cancer compared to close non-cancerous breast tissues(  $p > 0.001$ ). In addition the previous studies recorded that phosphates of regenerating liver-3 repressed ITGA2 expression in ovarian cancer cells [16] and other study COX2 increased active ITGA2 expression during the ep1/plc/pkca2 c-sre/ nf.kb signal transduction cells [17].

#### 3.1.2. Serum levels of hormones

In this study the mean of progesterone concentration in serum showed a significant increasing in patients ( $6.319 \pm 0.75$ ) ng/ml compared to control ( $3.206 \pm 1.08$ ) ng/ml ( $P < 0.05$ ). The prolactin recorded a highly significant increasing in patients ( $24.89 \pm 3.26$ ) ng/ml compared to control group ( $5.833 \pm 1.41$ ) ng/ml ( $P < 0.01$ ). As well as the estradiol observed a higher significant decreasing difference level in patient ( $540.88 \pm 17.97$ ) pg/ml compared to control ( $635.79 \pm 36.03$ ) pg/ml ( $P < 0.01$ ) as shown in Table 2.

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**Table (2):** Compare between patients and control in levels of hormones

The group	Mean $\pm$ SE		
	Progesterone ng/ml	Prolactin ng/ml	Estradiol pg/ml
Patients	6.319 $\pm$ 0.75	24.89 $\pm$ 3.26	540.88 $\pm$ 17.97
Control	3.206 $\pm$ 1.08	5.833 $\pm$ 1.41	635.79 $\pm$ 36.03
T-Test	2.932 *	11.734 **	75.298 **
P-value	0.0378	0.0018	0.0114

\* (P<0.05) significant, \*\* (P<0.01) ,high significant .

### 3.1.2. Progesterone level in serum

The present study showed a significant increasing in level serum of progesterone hormone in patients (6.319  $\pm$  0.75) as compared with control (3.206  $\pm$  1.08) under P<0.05. Progesterone is one of ovarian steroid hormones, previous studies have found that progesterone hormone is very important as a risk factor for breast cancer occurring in mice [18]. as well as it has been recorded that progesterone receptor (PR) expression is utilized as biomarker of estrogen receptor  $\alpha$  (ER $\alpha$ ) function and as a biomarker of breast cancer prognosis, it was also supposed that the elevated level of progesterone in serum perhaps represent a danger factor for breast cancer occurring, and it may have a role in initiation of cancer [19]. The current study was disagree with Kaaks *et al* [20] which showed a non-significant association of progesterone with breast cancer danger via menstrual cycle phase or via tumor receptor status. Although a possible risk increasing with the highest estradiol, Dowett [21] recorded that the low levels of progesterone in obese premenopausal women are responsible for the reduction of incidence of breast cancer in these women. Pervious study showed that serum progesterone levels represent a beneficial biomarker for predicting cancer histology preoperatively, which would help therapy planning While Serum progesterone levels were significantly elevated in postmenopausal women with mucinous ovarian cancer . In these women [22].

### 3.1.3. Prolactin level in serum

Prolactin (PRL) hormone plays a significant role in the development of the mammary gland and terminal diversity of the mammary epithelial cells [23]. the result of the Present study showed that prolactin level in serum recorded a high significant increasing in patient compared to control , (so we can suggest that the increasing level of prolactin in serum linked with breast cancer .And consider it a biomarker to detect the breast cancer prognosis) as shown in (Table 2). Our study disagree with Nyante *et al* [24]which showed alter serum prolactin levels were not associated with breast cancer risk ,while present study agree with Tworoger [25] which supposed that prolactin in serum is positively related with breast cancer risk. As well as PRL expression was significantly (P<0.01) linked with long distant metastasis-free survival in breast cancer patients [23] .Our current study was agree with Tikk *et al* [26] which suppose that there was a relation between serum level prolactin and invasive type of breast cancer to the outcome of in situ breast cancer. Clendenen *et al.* [27] which also suppose that prolactin perhaps linked with increased danger of ovarian cancer.

### 3.1.4. Estradiol Level in serum

17 $\beta$  Estradiol (E2) is the primary form of estrogen, a female sex hormone that is produced via the ovaries and important involved in women's monthly menstrual cycle [28] .Our study showed that the serum level estradiol (E2) was very low in breast cancer patients . Our study data was agree with Honma *et al* [8] which revealed that the Estradiol level in

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the serum was obviously lower in breast cancer patients. This study disagree with Kakugawa *et al* [29] which appeared that tissue estradiol (E2) is associated with growth of receptor – positive breast cancer. Also our data was disagreeing with Pasqualini *et al* [30] who revealed that estrogen concentration are higher within breast tumor tissue than in serum. Our study showed that the concentration Estradiol become a lower in women with breast cancer. Anthers recent study showed that a higher serum E2 level was related with an increasing danger of postmenopausal breast cancer [31]. Therefore, local estrogen synthesis from circulating steroid hormone precursors via steroid-forming and steroid-inactivating enzymes may be significant to drive ovarian cancer progression in women postmenopausal [32].

### 3.2. The level of trace elements in the serum

The result revealed that zinc has a highly significant difference in patients ( $39.92 \pm 3.44$ )  $\mu\text{g/dl}$  as compared with control ( $92.81 \pm 2.69$ )  $\mu\text{g/dl}$ . Zinc has a significant decreasing ( $P < 0.01$ ). As well as vitamin C showed a significant decreasing in patients ( $3.85 \pm 0.48$ ) ppm as compared with control ( $5.72 \pm 0.49$ ) ppm ( $P < 0.05$ ) as shown in Table 3.

**Table (3):** Compare between patients and control in levels of Zinc and Vitamin C.

The group	Mean $\pm$ SE	
	Zinc $\mu\text{g/dl}$	Vitamin. C ppm
Patients	$39.92 \pm 3.44$	$3.85 \pm 0.48$
Control	$92.81 \pm 2.69$	$5.72 \pm 0.49$
T-Test	12.641 **	1.786 *
P-value	0.0001	0.0406

\* ( $P < 0.05$ ) significant , \*\* ( $P < 0.01$ ) high significant .

#### 3.2.1. Zinc Level in serum

Zinc is a trace element that is pivotal for the function of several cellular process and perhaps play a serious role in cancer etiology [33]. The present study revealed that the serum level of zinc has a highest significant decreasing in patients and control, present study was agree with Pavithra *et al* and Kuo *et al*. [38, 34] who showed that the serum level of zinc has a significant reduction in breast cancer patients. While it was disagreeing with Wu [37] which recorded a non-significant Variation in serum zinc concentration between patients and control. Many studies support a new idea about the role of zinc in the growth of pancreatic adenocarcinoma [35]. Epstein *et al* [36] study was suggested that high dietary absorption of zinc was linked with reduction of prostate cancer after diagnosis. Shankar and Prasad which revealed zinc has an essential role in polynucleotide transcription and thus in the progress of genetic expression. Zinc plays a central role in the immune system, affecting a number of aspects of cellular and humeral immunity [39]. The impairments of immune defense are so far the only clearly demonstrated sign of mild zinc deficiency in human. Zinc is essential for cell proliferation, differentiation, regulation of DNA synthesis and mitosis. Zinc can modulate cellular signal recognition, second messenger metabolism, protein kinase and protein phosphatase activity and it may stimulate or inhibit transcription factor which required in signal transduction [40, 41]. We can suggest that the low zinc level in patient has a role in early event breast cancer occurring and it may associate with danger breast cancer type.

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### 3.2.2. Vitamin C level in serum

Ascorbic acid was first specified in vegetables, fruits (citrus), and adrenal glands. It was at a later time named vitamin C, Vitamin C is very important factor to human health. This vitamin cannot be created via humans, there for it is major that vitamin c be combined into our diet [42]. The present study showed a significant decreasing in breast cancer patient ( $3.85 \pm 0.48$ ) ppm compared with control ( $5.72 \pm 0.49$ ) ppm ( $P < 0.05$ ) as shown in (Table 3). The present data was in agree with Ray and Girija [43,44] which showed a lower mean and SE in serum level of vitamin C in patients as compared with control while it was disagree with Zhang *et al* [46] which revealed that there was a significant relation between vitamin c intake and breast cancer risk. So we need a lot of evidence to support the idea that vitamin c may has an essential role in breast cancer occurring and its supplementation may enhance the antitumor impact of chemotherapy or reduce its toxicity [11]. Harris *et al.* revealed that the significant increasing of vitamin c in serum level was linked with a lower danger of total death –rate and breast cancer particular death –rate [45].

### 3.3. Correlation coefficient of Integrin $\alpha 2$ ITGA2 and other parameters

Data in (Table 4) showed a significant correlation coefficient ( $P < 0.05$ ) among ITGA2 , progesterone and vitamin c while there was a non-significant correlation with other parameters (PR,ES, Zn, age).

**Table (4 ):**Correlation coefficient between ITGA2 and other parameters

Parameters	Correlation coefficient –r with ITGA2	P-value
<b>Progesterone</b>	0.24	0.0493 *
<b>Prolactin</b>	0.02	0.905 NS
<b>Estradiol</b>	0.09	0.384 NS
<b>Zinc</b>	-0.05	0.626 NS
<b>Vitamin. C</b>	0.26	0.0460 *
<b>Age</b>	0.14	0.180 NS
* ( $P < 0.05$ ) significant, NS: Non-Significant.		

This result was agreeing with Ding *et al* [15] who revealed that integrin  $\alpha 2$  ITGA2 protein level in breast tissue was not correlation with age group, Estrogen and progesterone. Sklidum *et al.* [47] who revealed that PR has a diverse function as a cytoplasmic signaling molecule and as a nuclear transcription factor. The loss of ITGA2 expression was helpful for malignant progression and metastasis [15]. Our data may explain the significant correlation among integrin, progesterone and vitamin C , was based on their roles whereas vitamin C regulate ECM which integrin considered one of its components, the effects of ECM are primarily mediated by integrin, a family of cell surface receptor that mediate the mechanical and chemical signals .These signals are regulate the activation of cytoplasmic kinases ,growth factor receptor, ion channels and control the organization of intracellular actin cytoskeleton. Many integrin signals may regulate cell cycle, directing cell to live or die, proliferate and differentiate as well as inhibition of cell growth by activation of transcription factor (NF-kappa) affected by vitamin C. Progesterone is also believe to mediate cell cycle progression through activation of cytoplasmic kinase and independently of direct regulation of transcription factors which involved in cell cycle progression; thus the loss of ITGA2 expression was helpful for malignant progression and metastasis.

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### 3.4. Associated of all parameters with clinical histological characteristics

#### 3.4.1. Integrin

As shown in Table 5 which illustrated the association of all parameters with histological characteristic, there was no significant difference and the result of the tumor histological type, stage, grade, age groups were (25.04±7.67+++ , 34.12±0.00+, 29.76±7.22+++ , 23.82±4.96+, 27.54±6.21++ , 26.03±2.96+++ , 22.50±2.17+ , 26.24±3.84+++ , 26.22±3.75+++ , 33.17±5.88+++ , 22.68±4.07+ , 27.29±8.64++) respectively. Our study showed that ITGA2 Protein level in serum was no association with all data, this result was agreeing with Ding *et al* [15] who revealed that ITGA2 protein level was not related to TNM stage, histological grad, age group.

**Table (5):** Association of serum integrin  $\alpha 2$  ITGA2 (ng/ml) level with Clinical histological characteristics.

Characteristic	NO	SE±Mean	Value LSD
<b>Histilologic subtype</b>			
<b>Ductal</b>	67	25.04±7.67 (+++)	17.348 NS
<b>Lobular</b>	1	34.12±0.00 (+)	
<b>Grade</b>			
<b>1</b>	4	29.76±7.22 (+++)	8.048 NS
<b>2</b>	46	23.82±4.96 (+)	
<b>3</b>	18	27.54±6.21(++)	
<b>stage</b>			
<b>BII</b>	46	26.03±2.96 (+++)	9.975 NS
<b>AII</b>	9	22.50±2.17 (+)	
<b>CIII</b>	7	26.24±3.84 (+++)	
<b>AIII</b>	6	26.22±3.75 (+++)	
<b>Age (25-55)</b>			
<b>Less than 35</b>	16	33.17±5.88(+++)	14.478NS
<b>35-45</b>	30	22.68±4.07(+)	
<b>More than 45</b>	22	27.29±8.64(++)	
<b>NS :Non-significant</b>			
<b>Low (+), medium(++) ,high (+++)</b>			

#### 3.4.2. Progesterone

The result of the present study showed a non-significant differences in association between progesterone serum level and the histological properties which included histological type ( ductal and Lobular) the result of Mean ± SE for the progesterone serum level were (6.32 ± 2.71 , 6.12 ± 0.00) respectively, grade 1,2, 3 (6.13 ± 1.97, 5.43 ± 2.03, 8.59 ± 2.94) respectively , while there was a significant difference in association between zinc with stage II B,II A,III A, III C the result was (5.66 ± 0.81, 6.22 ± 1.04, 14.38 ± 1.16, 7.74 ± 1.13) respectively and for Age group <35,35-45,> 45 the result was (2.74 ± 0.87, 5.75 ± 2.35, 5.01 ± 1.82) respectively as described in Table 4-8. There is no previous studies that agree or disagree with our finding, but according to the present result we may conclude that stage of breast cancer and age of patients affected with the level of progesterone and the most affected sub group was stage which has the highest mean (14.38 ± 1.16) and the most affected age sub group was < 35 which consider the youth age.

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**Table (6):** Association of serum Progesterone (PR) level with Clinical histological characteristics

Pathology	NO	Mean±SE	LSD value
<b>Histological type</b>			
Ductal	67	6.32 ± 2.71	11.835 NS
Lobular	1	6.12 ± 0.00	
<b>Grade</b>			
1	4	6.13 ± 1.97	5.490 NS
2	46	5.43 ± 2.03	
3	18	8.59 ± 2.94	
<b>Stage</b>			
II B	46	5.66 ± 0.81	6.031 NS
II A	9	6.22 ± 1.04	
III A	7	14.38 ± 1.16	
III C	6	7.74 ± 1.13	
<b>Age group</b>			
Less than 35	16	2.74 ± 0.87	9.877 NS
35-45	30	5.75 ± 2.35	
More than 45	22	5.01 ± 1.82	
<b>NS (non-significant)</b>			

**4.3.3. Prolactin (PLR)**

As shown in Table 7 .The association of prolactin level (PLR) with histological study showed a significant differences start with histological type (ductal ,lobular) were (25.14 ± 7.84, 8.99 ± 0.00) respectively , grade 1, 2, 3 (14.25 ± 2.68, 20.94 ± 2.77, 37.14 ± 5.63) respectively (P< 0.05), while it has been recorded a non-significant association between all stage I B,II A,III A, III C the result was (27.49 ± 2.67, 18.41 ± 2.58, 24.73 ± 2.61, 17.73 ± 3.42) Respectively, and finally for Age group < 35,35-45,>45 (15.89 ± 3.78, 21.28 ± 6.52, 23.88 ± 5.94) Respectively. This study was agreeing with Hachim *et al* [23]. Which it was disagree with Hachim *et al*. [23] who estimated the concentration of prolactin in tissue and recorded an association between PLR and histological outcome except the stage which showed a non-significant difference and has no association with PLR level in tissue [23]. As a conclusion there was a significant linked between prolactin and prolonged distant metastasis-free survival in breast cancer patients.

**Table (7):** Association of serum PRL (Prolactin) level with Clinical histological characteristics.

Pathology	NO	Mean±SE	LSD value
<b>Histological type</b>			
Ductal	67	25.14 ± 7.84	11.53 *
Lobular	1	8.99 ± 0.00	
<b>Grade</b>			
1	4	14.25 ± 2.68	13.905 *
2	46	20.94 ± 2.77	
3	18	37.14 ± 5.63	
<b>Stage</b>			
II B	46	27.49 ± 2.67	28.591 NS
II A	9	18.41 ± 2.58	
III A	7	24.73 ± 2.61	
III C	6	17.73 ± 3.42	
<b>Age group</b>			
Less than 35	16	15.89 ± 3.78	13.001 NS
35-45	30	21.28 ± 6.52	
More than 45	22	23.88 ± 5.94	
<b>* P &lt;0.05 Significant, NS (non-significant)</b>			

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### 3.4.4. Estradiol

As shown in Table 8, there was no association between Estradiol (E2) serum level with the tumor histological out come and there was no significant difference by using LSD the result was as follow, the Mean  $\pm$ SE of E2 for the histological type ( ductal ,lobular) were (541.50 $\pm$  138.2, 503.10  $\pm$  0.00) respectively. For Grade 1, 2, 3 were (477.70  $\pm$  116.3, 535.04  $\pm$  84.2 , 569.52  $\pm$  136.4 ) respectively. for stage II B,II A,III A, III C were (547.06  $\pm$  94.24 , 452.07  $\pm$  78.12 , 563.41  $\pm$  102.7, 496.53  $\pm$  85.61) respectively , and finally for Age group (<35,35-45,> 45) were (537.18  $\pm$  135.9 , 553.91  $\pm$  109.5, 528.73  $\pm$  97.2 respectively.

**Table (8):** Association of serum Estradiol (E2) level with Clinical histological characteristics.

Pathology	NO	Mean $\pm$ SE	LSD value
<b>Histological type</b>			
Ductal	67	541.50 $\pm$ 138.2	229.81 NS
Lobular	1	503.10 $\pm$ 0.00	
<b>Grade</b>			
1	4	477.70 $\pm$ 116.3	106.62 NS
2	46	535.04 $\pm$ 84.2	
3	18	569.52 $\pm$ 136.4	
<b>Stage</b>			
II B	46	547.06 $\pm$ 94.24	129.65 NS
II A	9	452.07 $\pm$ 78.12	
III A	7	563.41 $\pm$ 102.7	
III C	6	496.53 $\pm$ 85.61	
<b>Age group</b>			
Less than 35	16	537.18 $\pm$ 135.9	191.80 NS
35-45	30	553.91 $\pm$ 109.5	
More than 45	22	528.73 $\pm$ 97.2	

The present result was disagreeing with Shaaban *et al.* [48] who showed that the ER  $\beta$  (Estradiol)in tissue recorded a significant decreasing as compared with control (P=0.009) but there was a non-significant differences in association between E2 and grade of ductal carcinoma. While Fuque *et al.* [49] recorded a significant association between tumor grade and E2 receptor expression tissue. Estradiol displayed a borderline significant heterogeneity with breast cancer risk diagnosed for age above 50 [20].

### 3.4.5. Zinc

As shown in Table 9, the result of present study showed a non-significant differences in association between Zinc serum level and the histological properties which included histological type ( ductal and Lobular) the result of Mean  $\pm$  SE for the zinc serum level was (39.90  $\pm$  8.31, 41.54  $\pm$  0.00) respectively, grade 1,2, 3 ( 60.79  $\pm$  16.23,39.35  $\pm$  18.936.71  $\pm$  16.03)respectively , while there was a significant difference in association of zinc with stage II B,II A,III A, III C 34.54  $\pm$  4.51, 46.62  $\pm$  7.09 , 62.60  $\pm$  5.85,28.54  $\pm$  5.02) respectively and Age group <35,35-45,> 45 (58.51  $\pm$  12.73, 34.06  $\pm$  9.24, 40.95  $\pm$  11.50) respectively P<0.05. There are no previous studies that agree or disagree with the present data, but according to the present results we may conclude that stage of breast cancer and age of patients affect with level of zinc and the most affected sub group was stage III C which has the lowest mean (28.54  $\pm$  5.02) and the most affected age sub group was 35-45 which consider the youth age.

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**Table (9):** Association of serum zinc level with Clinic histological characteristics.

Pathology	NO	Mean±SE	LSD value
<b>Histological type</b>			
Ductal	67	39.90 ± 8.31	23.212 NS
Lobular	1	41.54 ± 0.00	
<b>Grade</b>			
1	4	60.79 ± 16.23	24.688 NS
2	46	39.35 ± 18.9	
3	18	36.71 ± 16.03	
<b>Stage</b>			
II B	46	34.54 ± 4.51	27.438 *
II A	9	46.62 ± 7.09	
III A	7	62.60 ± 5.85	
III C	6	28.54 ± 5.02	
<b>Age group</b>			
Less than 35	16	58.51 ± 12.73	22.411 *
35-45	30	34.06 ± 9.24	
More than 45	22	40.95 ± 11.50	
*P<0.05 significant			

**3.4.6. vitamin C (ascorbic acid)**

As shown in Table 10. The present study revealed that there was no association between vitamin C and histological characteristics and there was no significance difference by using LSD value. The result of the histological type (ductal, Lobular) was (3.86 ± 1.04, 3.13 ± 0.00) respectively, Grade 1,2,3 was (4.17 ± 0.96, 3.27 ± 1.15, 5.31 ± 1.33) respectively, stage II B, II A, III A, III C was (3.73 ± 0.77, 4.06 ± 0.83, 4.99 ± 0.94, 3.94 ± 0.71) respectively and finally the Age group (<35,35-45,>45) was (6.908 ± 2.57, 4.60 ± 2.07, 5.93 ± 2.88) respectively.

**Table (10):** Associated of vitamin C level in serum with Clinical histological characteristics

Pathology	NO	Mean±SE	LSD value
<b>Histological type</b>			
Ductal	67	3.86 ± 1.04	8.115 NS
Lobular	1	3.13 ± 0.00	
<b>Grade</b>			
1	4	4.17 ± 0.96	3.783 NS
2	46	3.27 ± 1.15	
3	18	5.31 ± 1.33	
<b>Stage</b>			
II B	46	3.73 ± 0.77	4.024 NS
II A	9	4.06 ± 0.83	
III A	7	4.99 ± 0.94	
III C	6	3.94 ± 0.71	
<b>Age group</b>			
Less than 35	16	6.908 ± 2.57	4.775 NS
35-45	30	4.60 ± 2.07	
More than 45	22	5.93 ± 2.88	
NS, non-significant			

The present data was disagree with the study by Ray [43] who showed that the vitamin C recorded a significantly decreasing in serum level in progress stages of breast

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cancer ( $p < 0.01$ ), also it was disagree with Greenlee *et al.* [50] which recorded a significantly increasing in serum level of vitamin C related with stages and age group. While Gallie [44] recorded that the serum level of vitamin C will increasing with the progress stage of the disease.

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