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Evaluation Of The Level Of Cancer Antigen CA15-3 And CRP Along With Some Immunological And Physiological Variables In Patients With Breast Cancer In Al-Muthanna Governorate.

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Abstract
This study was conducted in the laboratories of Al-Hussein Teaching Hospital and some private laboratories in the city of Samawah in Al-Muthanna Governorate for a period from 1/15/2024 to 3/15/2024. The study included (80) samples of women of reproductive age, ranging in age from (25-70). year, and were divided into two groups:
• **Patient group:** (40) samples of patients with breast cancer.
• **Control group:** (40) samples of healthy women.
The pathological cases of women with breast cancer were confirmed after conducting clinical examinations and referring them to the specialist doctor and performing an ultrasound examination. After that, blood was taken from both groups (patients and healthy people) and separated using a centrifuge. Then the level of cancer antigen was measured. CA15-3 and CRP to confirm whether they have breast cancer, in addition to measuring immune and physiological variables. The results of the current research showed a significant increase in each of the diagnostic, immunological, and physiological indicators in the blood serum of both groups, at a probability level of $P \leq 0.05$.

Key words: Breast cancer, CA15-3, CRP, IL-6, TNF-α.

Introduction

Cancer is known as an uncontrollable disease that has the ability to grow very quickly, unlimited fission of various body cells, and the ability of its cells to attack and destroy nearby body tissues and destroy them, or move through the blood to distant body tissues. This is called a malignant tumor, and there is a type. Another type of cancer characterized by specific growth and its inability to metastasize and attack different body cells. It is called a benign tumor. This type can develop in the body and divide into several divisions, ultimately leading to malignant cancer [(1).]

Breast cancer is the second most common cause of death among women, as surgical resection is a major treatment method, and local recurrence of the tumor plays an important role in the overall oncology results with regard to survival for each type of cancer [(2)], so more than half of cancer cases In Iraq, it is in the breast [(3)], as it was found in Iraq that breast cancer is the first malignant tumor that affects society and is the main cause of cancer-related deaths among Iraqi women and the second main cause in general among men and women after bronchogenic cancer [(4)].

Breast cancer is sometimes considered a metastatic disease, meaning the disease spreads to other parts and locations of the body, and its symptoms vary depending on the location to which the tumor has spread. Among the common sites to which breast cancer spreads are the brain, liver, lungs, and bone [(5)], in addition to the indicators that Indicators of the presence of metastatic breast cancer are unexplained weight loss, joint and bone pain, high fever, jaundice, and other neurological symptoms[(6)]. The methods of diagnosing breast cancer depend on clinical examination first, physical tests second, and computed tomography third, in addition to the use of ultrasound and laboratory tests. These laboratory tests include measuring the level of tumor markers, measuring the level of cancer antigen CA15-3, in addition to measuring growth factors and measuring factor receptors. Human Growth HER2 Human 2 Epidermal Growth Factor, in addition to measuring the CRP level, as these examinations and tests provide the treating physician with predictions, diagnostic possibilities, and complete information to begin the treatment phase for the patient [(7).]

Cancer antigen CA15-3 is one of the naturally produced proteins found in breast tissue in the human body. The level of this cancer antigen increases in the event of a cancerous tumor in the breast [(8).] The level of CA15-3 increases in the case of metastatic breast cancer, pancreas cancer, and lung cancer. And rectum and liver cancer, as well as it can increase in some benign tumors in the breast and liver. CA 15-3 increases in less than 33% in breast cancer patients of stages II and I [(9).] The level of carcino antigen CA15-3 rises in more than 79-92% of patients with cancer, especially advanced breast cancer, as the use of this antigen is very useful to know the pathological stage that breast cancer has reached in order to begin treatment, as its decrease is slight in relation to For successful treatment, therefore, a period of investigation is required to confirm the significant decrease in CA15-3 [(10).]

Interferons are divided into interferon-alpha and interferon-gamma, as interferon-alpha has been identified as a protein that interferes with the immune response in the body, especially in cases of various viral infections [(11)]. The importance of these immune kinetics is prominent in the types of natural and acquired immunity in the body, as they intervene in many infectious, viral, and inflammatory diseases, injuries, infectious diseases, and blood poisoning, but their mission is not limited to the immune system only, but also enables them to communicate between the different cells of the body

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through genetic development in them [12], which in turn can help the differentiation and proliferation of immune cells, their migration, and stimulate them to produce other compounds depending on the type of their stimulus, as cellular motility includes multiple types, including lymphatic motility, including lymphokines, which are produced from lymphocytes, monokines, which are produced from monocytes, and interferons alpha and beta, which are produced in the Viral infections and colony stimulating factors are divided into interleukins such as IL-6, IL-7, IL-15 [13].

IL-6 stimulates cancer cells by enhancing anti-apoptotic and proangiogenic proteins in cancer cells by regulating estrogen in the breast [14]. When cancer cells are exposed to Interleukin-6, they show malignant features such as invasion of extracellular areas and cell resistance to angiogenesis. IL-6 has an important role in determining tumor behavior, such as tumor growth, tumor proliferation, tumor spread, and formation of blood vessels in the tumor, and also plays an important role in interpreting the pathological stage of breast cancer [15].

Fibronectin is considered one of the glycoproteins that have a high molecular weight. Fibronectin usually plays an important and beneficial role in the body. It helps in forming supports that support and strengthen connective tissue cells in the body, which facilitates the repair of tissues after their destruction. However, after a stroke, the reaction of fibronectin is It is very strong and somewhat tangible, so it polymerizes and helps in the production of a lot of intercellular connective matter in the body's various tissues. It also causes an increase in the production of clumped, functionally ineffective myofibroblasts that harm the body, especially the heart muscle [16]. Fibronectin plays an important role in tumorigenesis and malignant progression Oncogenic FN plays a tumor suppressor role, while it is pro-metastatic and associated with poor prognosis. , as well as FN matrix deposited in tumor microenvironments promote tumor progression but are paradoxically associated with improved prognosis [17]. In addition to magnetic resonance imaging, which targets fibrin-fibronectin complexes in breast cancer, as cancer cells invade the primary tumor to distant organs through epithelial transition to mesenchyme and transmit signals from one place to another, they spread throughout the body [18]. Through the increase in diagnostic and immunological indicators, the goal of the current research is to Evaluation of the level of cancer antigen CA15-3 and CRP along with some immunological and physiological variables in patients with breast cancer in Al-Muthanna Governorate.

Collection of specimens

This study was conducted in the laboratories of Al-Hussein Teaching Hospital and some private laboratories in the city of Samawah in Al-Muthanna Governorate for a period from 1/15/2024 to 3/15/2024. The study included (80) samples of women of reproductive age, ranging in age from (25-70). year, and were divided into two groups:

- **Patient group:** (40) samples of patients with breast cancer.
- **Control group:** It was (40) samples of healthy women

The pathological cases of women with breast cancer were confirmed after conducting clinical examinations and referring them to the specialist doctor and performing an ultrasound examination. After that, blood was taken from both groups (patients and healthy people) and separated using a centrifuge. Then the diagnostic and immunological indicators were measured. . The results of the current research showed a significant increase in each of the diagnostic, immunological, and physiological indicators in the blood serum of both groups, at a probability level of $P \leq 0.05$.

- **Estimating levels of diagnostic indicators in blood serum:**

The level of the hormone (cancer antigen CA15-3 and CRP) was estimated using the ELISA technique (Sandwich), where the antibodies to the cancer antigen CA15-3 and CRP were pre-fixed in the holes of the microtiter plate. The blood serum of the samples is added to the holes of the plate to bind to the cancer antigen CA15-3. 3 and CRP in the sample with antibodies treated with biotin and coated the holes, after which their Streptavidin-HRP is added to each well in succession and incubated, the pits are then washed with wash buffer to remove unbound antibodies. The matrix solution is then added so that the color develops in proportion to the level of cancer antigen CA15-3 and CRP in the serum, The reaction stops after adding the acidic Stop solution to it. The absorbance of each pit is then read at Wavelength 4500.

- **Estimating the levels of immune and physiological indicators in blood serum:**

The concentration of each of the levels of (FN, TK-1, TNF-α, and IL-6) was measured by adopting the ELISA technique (Sandwich) and by following the ready-made steps indicated in the custom analysis kit, and it differs from one device to another and according to its manufacturer.\

Statistical Analysis

The process of collecting data for the samples used for the study and analyzing them statistically was done using the SPSS system by extracting the arithmetic mean and standard deviation. The test was also used to analyze the differences between the group of patients and healthy people. Significant differences were chosen for these groups under a probability level of $P \leq 0.05$.

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Result and Desiccation

• Measuring the levels of diagnostic, immunological and physiological indicators in the blood serum of both groups (patients and healthy people):

Table No. (1) shows the mean ± standard deviation of diagnostic, immunological, and physiological indicators in the blood serum of the two study groups.

Groups / Parameter	Mean ± SD		P-Value
	Control n=40	Patients n=40	
CA15-3 (U/ml)	5.18±0.87	50.68±17.91	P≤0.05
CRP (ng/ml)	10.79±1.67	5.95±0.67	P≤0.05
IL-6 (pg/ml)	28.41±10.02	47.79±12.09	P≤0.05
TNF-α (ng/ml)	65.32±21.97	118.67±31.27	P≤0.05
Fibronectin (mg/L)	1170.3±304.7	3918.2±982.6	P≤0.05
TK-1 (ng/ml)	0.41 ± 0.089	1.91 ± 0.37	P≤0.05

The results of the current study for patients with breast cancer compared to healthy women showed a significant increase in each of the diagnostic, immunological, and physiological indicators in the serum of both groups (patients and healthy people), at a probability level of $P \leq 0.05$. As in the following figures.

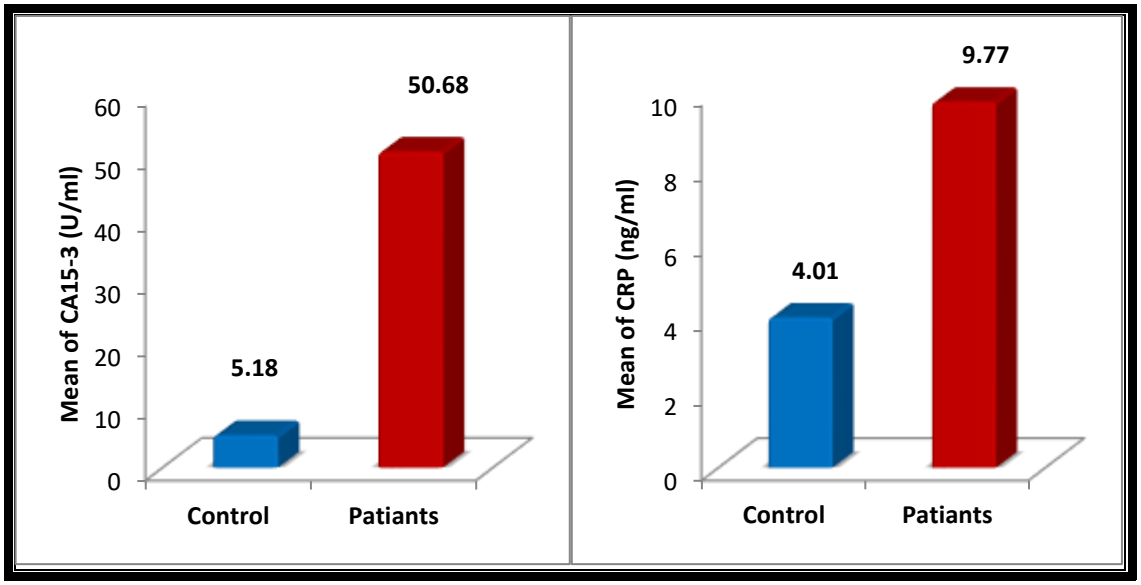

Figure (1) : CA15-3 in the blood sera of the samples under study

Figure (2) : CRP in the blood sera of the samples under study

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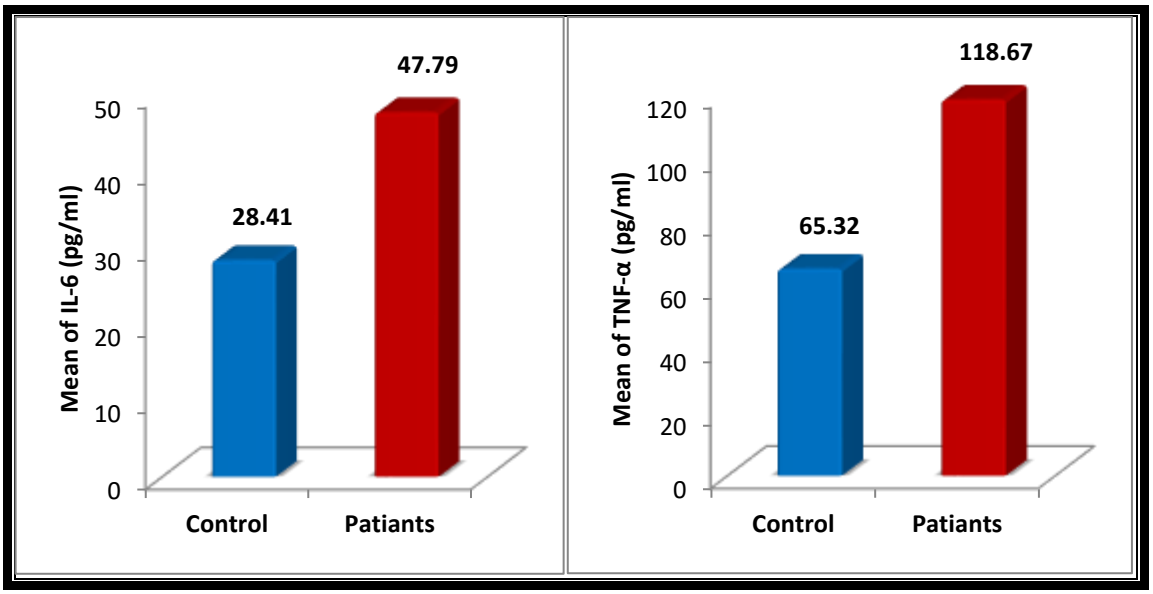

Figure (3) : IL-6 in the blood sera of the samples under study **Figure (4) : TNF-α in the blood sera of the samples under study**

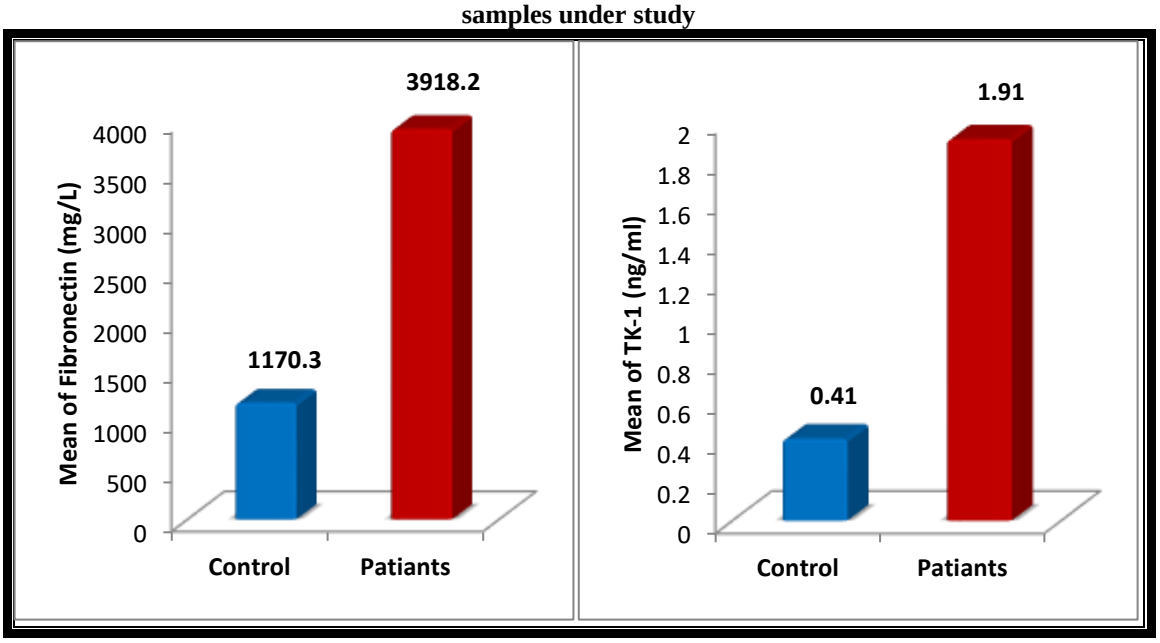

Figure (5) : FN in the blood sera of the samples under study **Figure (6) : TK-1 in the blood sera of the samples under study**

Desiccation

Cancer antigen (CA15-3) and CRP are considered one of the diagnostic markers that help treating doctors in early diagnosis of breast cancer, starting the stage of treating patients, and estimating important predictive factors for them. A study showed that female patients with breast cancer have increased levels of cancer antigen (CA15-3). and CRP [19].

The current research results are consistent with the results of the study of Hamdi et al [20] and the results of the study of Feng et al [21], who indicated in their study that the cancer antigen CA15-3 is excessively high in women with breast cancer, which indicates the presence of a chance for the disease to develop or spread to the organs of the body. The other is that the CA15-3 test is one of the most important requirements for diagnosing cancers, including breast cancer, and when a change occurs in the level of CA15-3, these changes are reflected in the stage of the disease if tumor markers are used in clinical practice, and thus this will lead to giving the appropriate treatment to indicate its effectiveness in the body. Therefore, CA15-3 is the most suitable marker with high specificity, moderate sensitivity, and appropriateness in predicting distant malignant tumors that occur in the body,Therefore, most studies indicated that CA15-3 is an important diagnostic biochemical marker for patients with breast cancer [22,23].

As for the other diagnostic indicator, it is CRP, as the results we obtained agree with the findings of Panis and his group [24], Allin and his group [25], and Celik and his group [26], who indicated in their study an increase in the level of CRP in patients with breast cancer compared to the control group. The reason for the increase in the concentration of CRP in

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The serum of women with breast cancer is due to chronic inflammation, which is one of the main factors that contribute to the development and progression of the carcinogenesis process, as inflammatory pathways play an important role in causing breast cancer.

C-reactive protein is an inflammatory protein that interacts in the acute phase. It is synthesized in liver cells in response to cytokines that are released from leukocytes within the tumor microenvironment. Thus, CRP concentrations in the blood circulation increase in response to acute inflammation and it has prognostic value in breast cancer patients [27,28].

As for interleukin-6, its results agreed with the results of Hussein et al [29] and Thwani [30], which showed that the level of IL-6 increased in the serum of women with breast cancer compared to the control group. Interleukin IL-6 plays an important role in the development of some types of cancer, including breast cancer, as it works to inhibit programmed cell death and also works to stimulate the formation of blood vessels in various tumors in the body [31]. The level of IL-6 in the serum of patients increases as the tumor advances and spreads in the body. This is because IL-6 acts as an anti-inflammatory, and when the tumor advances, the body tries to combat the tumor by increasing the level of IL-6 in the serum, as cytokines collect at the tumor site with white blood cells. To begin the process of repairing tissues affected by the tumor, this leads to an increase in the level of interleukin in the serum [32].

In addition to TNF-a, its results agreed with the results of both Al-Hassan et al [33] and the results of Alkhafaf et al [34], which showed an increase in the level of TNF-a in patients with breast cancer compared to the control group. The current study also agrees with a study conducted On female albino rats by Aldulaimy et al [35]. TNF antagonists act as therapeutic agents in solid tumors, but patients with high levels of TNF-a fail to respond to infliximab, due to the body's consumption of circulating TNF antagonists and tumor progression [36]. TNF activates Nuclear Factor Kappa B. NF-κB when exposed to cancer cells in the body [37], as TNF-a plays an important and decisive role in treating inflammation, regulating immunity in the body, cell differentiation, and tumor formation [38].

As for fibronectin, the results of his study agreed with the findings of Libring.S and his group [39], Zhuoran Gong and his group [40], and Aparna Shinde [41], which showed an increase in the protein fibronectin in women with breast cancer compared to the control, as fibronectin is considered a glycoprotein. Glycoprotein is secreted when clots form in the body [42]. Fibronectin usually plays an important and good role in the body. It helps in forming supports that support connective tissue cells in the body, which facilitates the repair of tissue expansion after infection. However, after infection with breast cancer, the reaction of fibronectin It is strong and tangible, so it polymerizes and helps produce a lot of intercellular matrix in the affected area. It also causes an increase in the production of clumped and dysfunctional fibroblasts found in breast cancer [43].

As for the thymidine kinase enzyme, its results agreed with the findings of Mao et al (2002), where a high level of TK1 concentration was observed in the sera of women with breast cancer in relation to the tumor stage and tumor grade, as TK1 can be a more accurate marker for estimating cell proliferation. Malignancy in body and behavior in breast cancer [44]. Mao also observed that the level of thymidine kinase in women with breast cancer before surgery was twofold higher than in women with breast cancer after surgery [45]. Although the patients' preoperative TK1 values were much higher than those of healthy controls, the most likely explanation for the reason for their elevation is that TK1 differently reflects the degree of tumor development and growth in the body [46]. Also, determining the level of TK1 indicates that it is a useful marker when judging the therapeutic effect for breast cancer patients.

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