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Evaluation of the Relationship among Survivin and Some Biochemical Markers in Women with Breast Cancer

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ABSTRACT:

The present study was conducted on a group of women with breast cancer (60 women) and a group of healthy women as a control group (30 women) aged (27-85) years. Samples were collected from women with breast cancer from the Teaching Oncology Hospital - Medical City, Baghdad for the period from the first of October 2023 until the end of February 2024. The activity of servivin was asses and the level of glutathione, glutathione peroxidase, malondialdehyde and the following results were obtained:

1-There was a significant increase in the group of breast cancer women for both servivin, and malondialdehyde compared to the control group.

2- There was a significant decrease in the level of glutathione-and glutathione peroxidase .

3-The existence of a significant correlation between survivin and each of GSH and GPX. **Conclusions:** The results of the present study showed a significant increase in the level of survivin in women with breast cancer in conjunction with a significant correlation with GSH, GPX, MDA and BMI, which supports the possibility of considering survivin as an indicator for breast cancer diagnosis.

Key words: Survivin, breast cancer, glutathione, glutathione peroxide, malondialdeyde .

INTRODUCTION:

Breast cancer poses a significant risk to women, and with high rates of morbidity and mortality, due to the lack of reliable diagnostic models, doctors find it difficult to develop a treatment regimen capable of increasing the life expectancy of a patient. Breast cancer needs to be detected in the early stages, so steps must be taken to stop this disease [(1)]. The development of breast cancer is a multi-step process involving multiple types of cells, and its prevention remains a challenge in the world, early diagnosis of breast cancer is one of the best ways to avoid its complications in some developed countries, the relative survival rate of 5 years for breast cancer patients exceeds 80% due to early prevention., Significant progress has been made in understanding breast cancer as well as in developing methods of prevention where the mechanisms of pathogenesis and resistance of tumors to drugs have been detected from During the discovery of breast cancer stem cells and many genes associated with breast cancer have also been found, people have more drug options for the

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chemoprevention of breast cancer, while biologically has recently been developed to improve the quality of life of patients[2].

Cancer is a disease that results from the uncontrolled growth of a group of cells that lead to the formation of cells that are not subject to the rules of normal cell division, these cells continue to grow to form other new abnormal cells capable of invading neighboring tissues and spreading to different locations of the body by penetrating the wall of blood vessels and lymphatic [3]. Cancer arises from one abnormal cell that moves through multiple transformations from the normal state to the state of malignant tumor, and the normal non-cancer cells grow and divide into additional cells, and are subject to a limited number of division cycles in a controlled way, when cells are damaged or become aged, they are subject to apoptosis or necrosis, and the interaction between genetic, physical, chemical and biological carcinogenic factors can disrupt this system, causing damage and As a result of these mutations, the cells multiply uncontrollably leading to tumor formation and that as a result of these mutations, cells multiply uncontrollably, leading to tumor formation and various types of cancer[4] .

Metastasis is the leading cause of most cancer deaths[5] , and metastasis means the spread of cancer cells from their site of origin to a distant organ[6], the tumor in its origin is called the primary tumor while the tumor that has spread to other sites is called the secondary tumor[7]. Due to the remarkable speed of development in breast cancer, many studies aimed to discover new biomarkers to reach early diagnosis and start treatment quickly, thus increasing the chances of achieving a cure for the patient.

Survivin, a member of the family of apoptosis inhibiting proteins, is the subject of many research and studies related to cancer[8]. This protein, with a molecular weight of 16.5 kDalton, is encoded by the BIRC5 gene, first cloned in 1999 and detected in many malignant cases of tumors[9].

Other predictive markers are needed in clinical practice[10], as studies of the clinical and . molecular characteristics of tumors allow the design of more efficient treatment strategies and less toxicity [11]. In this context, the expression of antioxidant proteins in cancer cells has been evaluated as a predictive factor in response to cytotoxic therapies[12] .

Glutathione is a tri-peptide composed of the amino acids glycine, cysteine and glutamic acid. Glutathione plays an important role in the antioxidant system required to maintain the redox state of the cell, defend against free radicals and detoxify toxic compounds. Reduced glutathione (GSH) can be converted to oxidized glutathione (GSSG) during oxidative stress. The percentage of reduced glutathione can be considered as an indicator of redox state and a useful indicator of disease risk[13].

Glutathione peroxides contains selenium in a catalytic site and uses GSH as an electron donor to reduce H_2O_2 to H_2O, converting itself into its oxidized form, glutathione disulfide (GSSG) [14]. GSH is one of the most important factors of the cell's antioxidant defense system. Since it is combined with GPX, GSH plays a role in the removal of biological and carcinogenic alien agents [15]. High levels of GSH or GPX increase antioxidant capacity, as observed in many cancer cells. Although the mechanism and consequences of these changes are not

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clear[14], Also research has demonstrated that increased antioxidants in tumor mammalian tissue provide certain advantages for these cells compared to healthy tissue; the presence of these enzymes in tumor cells may represent a low-grade response to treatments that cause oxidative damage, such as radiation therapy and chemotherapy[16].

Malondialdehyde (MDA) is one of the hydrolysis products of lipid peroxide and is also formed as a product of the reaction of cyclooxygenase in prostaglandin metabolism. MDA may be involved in tumor enhancement because it can interact with functional groups of a variety of cellular compounds, including amino groups of proteins and nucleic acid bases bases of phospholipids and SH groups of sulfuryl compounds[17] .

MATERIAL AND METHODS:

The present study was conducted on a group of 60 women with breast cancer and 30 of healthy women as a control group aged (27-85) years. Samples were collected from women with breast cancer from the Teaching Oncology Hospital - Medical City, Baghdad for the period from the first of October 2023 until the end of February 2024.

Estimation of survivin , glutathione (GSH),glutathione peroxidase (GPx) and malondialdeyde (MDA) were estimated using readymade kits.

RESULTS AND DISCUSSION:

Estimation of Survivin:

The level of survivin was significantly elevated in women with breast cancer (235.452±31.762 pg/ml) (compared to the control group (158.273±36.124 pg/ml), as shown in Table (1) and Figure(1).

TABLE 1:shows MEAN± SD of Survivin, GSH, GPX and MDA

Parameter	Control Mean ± SD N=30	Patient Mean ± SD N=60	P - value
Survivin pg/mL	158.273± 36.124	235.452± 31.762	0.05
GSH ug/ml	13.628 ±1.124	6.532 ±2.599	0.05
GPX pmol/m	40.909 ± 3.076	24.413 ± 4.744	0.05
MDA ng/ml	6.048 ± 2.817	23.147 ± 4.508	0.05

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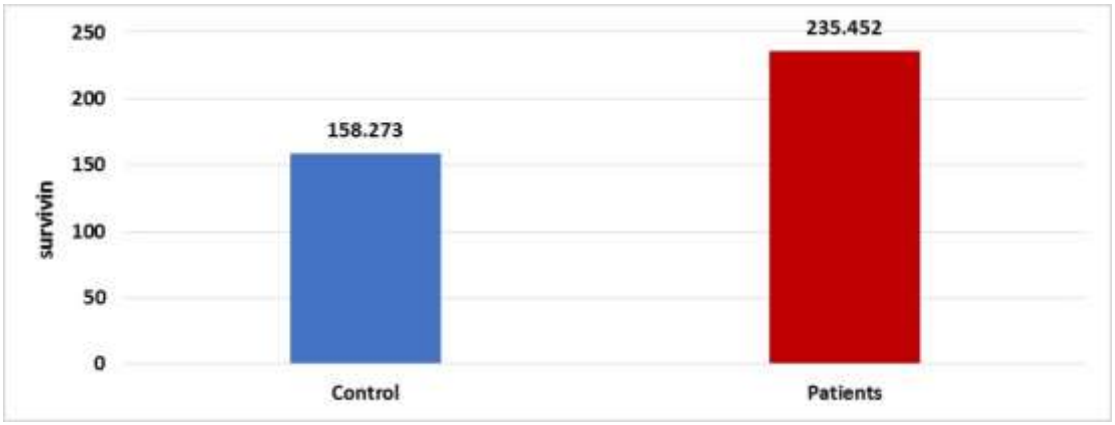

Figure 1 : shows difference in survivin level between patient and control

It is found that the level of survivin is significantly higher in the group of patients compared to the control group and the results of the current study are consistent with the results of Martínez-Sifuente etal, .2022[8] and Cao, Q. et al 2023 [18] which showed higher levels of survivin in women with breast cancer compared to healthy women. Survivin is a protein that plays an important role in the development of breast cancer by being an ideal target for inhibiting apoptosis, promoting mitosis, stimulating blood vessel growth and thus stimulating chemical resistance. These functions touch on the full range of tumor formation, including proliferation, migration, and invasion, and collectively facilitate malignant behavior [18]. Survivin is involved in tumor formation through various mechanisms, including inhibition of apoptosis, regulation of cellular mobility and cell cycle development, and participate in a variety of pathways such as p53, Wnt, hypoxia, TGF and Notch signaling pathways. However, the main aspect of survivin and its conjugation variants is its role in inhibiting apoptosis. The process of apoptosis is important in the formation of cancer[19].

Estimation of glutathione level:

The level of glutathione was significantly decreased in women with breast cancer (6.532±2.599ug/ml) compared to the control group (13.628±1.124ug/ml), as shown in Table (1) and Figure(2).

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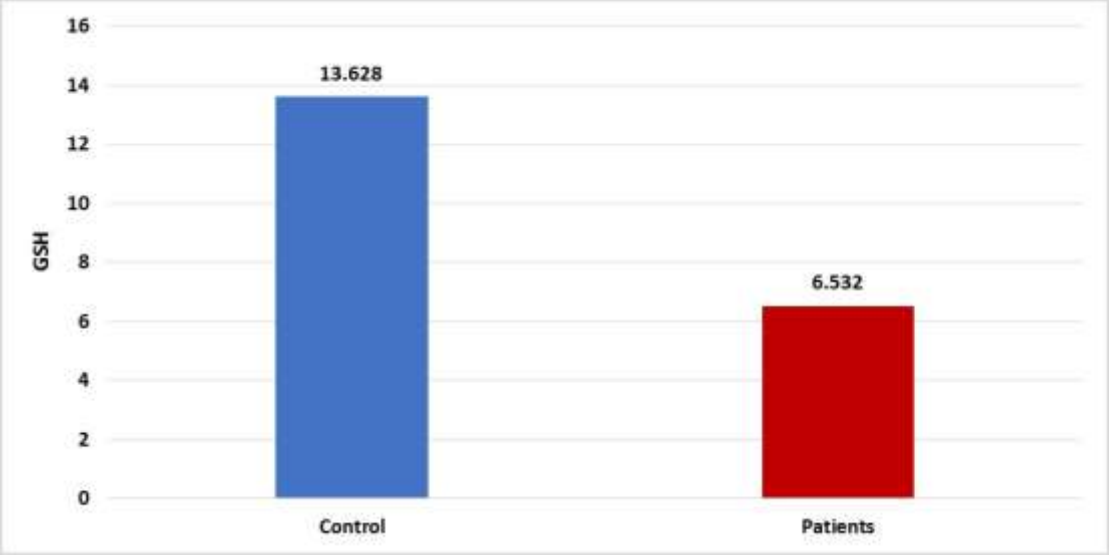

Figure 2: shows difference in GSH level between patient and control

The current study indicated a decrease in the level of glutathione in patients with breast cancer compared to healthy women and the results of the current study are consistent with some other studies such as Salman et al in 2020[20], and with Yeh et al in 2005[21], where a decrease in the level of glutathione was observed in women with breast cancer, where glutathione works to re-create some antioxidants due to its importance in fighting oxidative stress and preserving cells from cancerous diseases that affect the body. It protects liver cells from the effects of radiation or chemotherapy [22] who stated that Glutathione acts as a regulator of the cellular redox state and protects cells from damage caused by lipid peroxides, reactive oxygen and nitrogen species, and foreign substances. studies have highlighted the importance of glutathione in key signal transmission reactions as a controller of cell differentiation, proliferation, apoptosis, and immune function. Molecular changes in the glutathione antioxidant system and disturbances in glutathione balance have been shown to contribute to tumor initiation, progression and response to treatment. Thus, glutathione has protective and pathogenic roles. Although in healthy cells it is necessary to remove and detoxify carcinogens, decreased glutathione levels in cancer cells are associated with tumor progression and increased resistance to chemotherapeutic drugs[23]. The difference may be due to the continuous consumption of glutathione to be present in the serum of cancer patients in order to compete with oxidative stress in the cancer cell[24].

Estimation of glutathione peroxidase activity:.

The activity of the glutathione peroxidase was significantly decreased in women with breast cancer (24.413±4.744 pmol/ml) compared to the control group (40.909±3.076), as shown in Table (1) and Figure(3).

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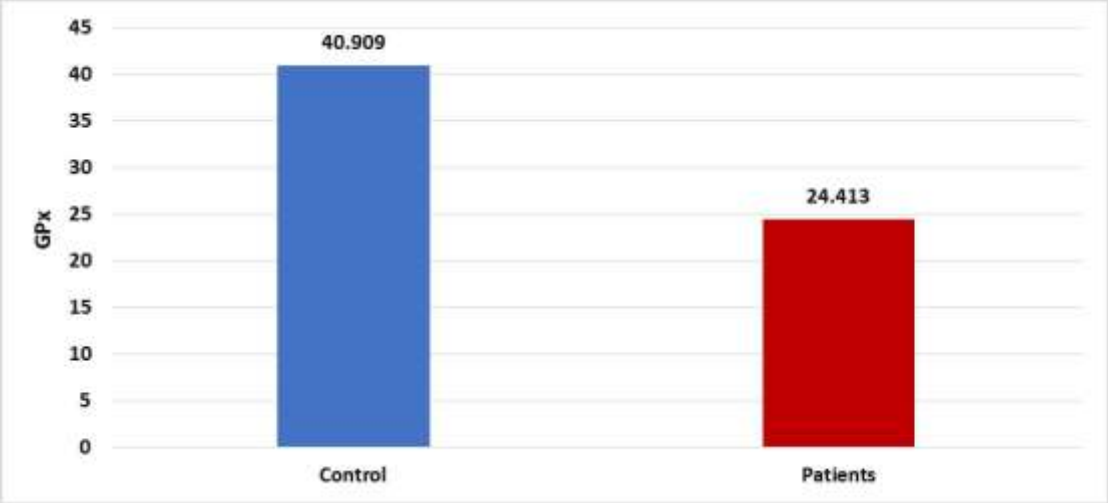

Figure(3): Activity of the glutathione peroxidase between patient and control.

The current study showed a significant decrease in the activity of the glutathione peroxidase in women with breast cancer compared to healthy women, and some studies agree with the results of the current study, which showed a decrease in the activity of glutathione peroxidase in patients with breast cancer, including the results of **Rajendra**& Kedari 2020 [25] and Zhang et al 2020[26], and this is identical to the results of the current study, which recorded a significant decrease in the group of patients compared to the control group, and this may be due to the work of antioxidant systems. glutathione peroxidase is one of the defense lines against free radicals in relation to enzymatic antioxidants[27] . Selenium deficiency may also cause GPx under synthesis as the enzyme is one of the proteins that are Seleno enzyme associated with selenium deficiency reduces the gene expression of GPx, especially GPx1, which is the symmetrical isomer associated with breast cancer [28].

Estimation of malondialdehyde level (MDA) :

The level of MDA was significantly elevated in women with breast cancer (2423.147±4.50 ng/ml) compared to the control group (6.048±2.817 ng/ml), as shown in Table (1) and Figure(4).

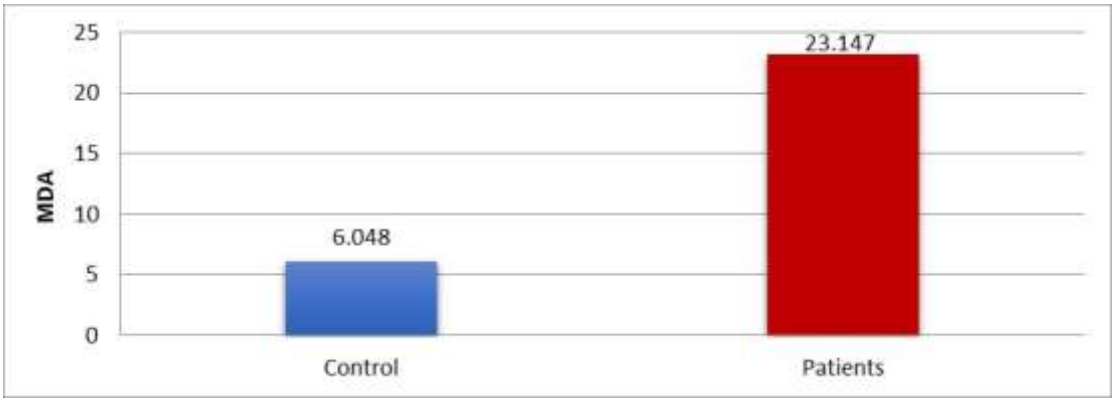

Figure (4): shows the level of MDA in breast cancer between patient and control.

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The MDA level is significantly elevated in the breast cancer women compared to control group and the results of the current study are consistent with the results of Yeh, C. C., et al. 2005[29] and Polat, M. F., et al 2002[30]; Who showed high level of malonedialdehyde in women with breast cancer. The results of the study also agree with the results of Mohamed et al in 2009[31] who explained that malonedialdehyde elevated in women with breast cancer due to the depletion of antioxidants as well as lipid peroxidation and increase of reactive oxygen species, because high malondialdehyde is a clear indicator of lipid peroxidation and increase free radicals and thus increase lipid oxidation. lipid peroxidation cause an increase in genetic mutations and an increase in cancerous tumors as well as increased cellular damage[32].

One study indicated that malonedialdehyde is elevated in women with breast cancer because unsaturated fatty acids are more susceptible to reactive oxygen species compared to other compounds such as proteins and DNA[33]. the changes in the level of malonedialdehyde depend on the stage of the disease and the age of the patient[34].

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