ISSN 2664-4142 (Print) & ISSN 2664-6749 (Online)
South Asian Research Journal of Pharmaceutical Sciences
Abbreviated Key Title: South Asian Res J Pharm Sci

| Volume-5 | Issue-4 | Jul-Aug- 2023 | **DOI: 10.36346/sarjps.2023.v05i04.002**

Original Research Article

Evaluation of the Role of Oxidative Stress and Vitamin D in Blood of Breast Cancer Women

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Article History
Received: 17.05.2023
Accepted: 20.06.2023
Published: 04.07.2023

Abstract: Breast cancer is one of the most common cancers in women, and it is the leading cause of cancer-related deaths around the world. It is the most common cancer diagnosed in Iraqi women. The obtained results show an increase in breast cancer incidence. The maximum rate of the disease occurred in women above 48 years. The incidence of cancers is closely related to the age group that was low in age 0-40 and increases rapidly with age increase due to obesity, the incidence of breast cancer increases with age that suggests may be due to DNA methylation which is one of the reasons behind increased BC with age, as it is a normal part of the aging process. The most essential reasons behind increased BC with age among Asians are poverty, poor dietary habits, and unhealthy lifestyle.

Keywords: Cancer, Breast cancer, DNA, Age.

INTRODUCTION

Cancer is defined by a loss of control over cellular growth and development, which results in excessive cell proliferation and spread. Breast cancer is one of the most common cancers in women, and it is the leading cause of cancer-related deaths around the world. It is the most common cancer diagnosed in Iraqi women [1, 2].

In women, breast cancer accounted for nearly 24.5% of all cases and 15.5% of cancer deaths in 2020, placing it global for both incidence and mortality [2]. Its etiology and causative factors are complex and interlinked which includes family history, gene susceptibility, hormone, diet, lifestyle factors and environmental exposures. The most significant risk factors for breast cancer include advanced age, high body mass index or obesity, exposure to tobacco, lack of physical activity, a high-fat diet, early menarche, a late age at the first full-term pregnancy, shorter breastfeeding intervals, use of hormonal menopausal therapy or oral contraceptives, breast density, and a family history of breast cancer [3]. Breast cancer is a multi-step process that involves several cell types, and it is still difficult to prevent globally. One of the most effective ways to avoid breast cancer is early detection [3-6].

Oxidative stress is a pathophysiologic imbalance induced in the body which is formed by the breakdown of the balance between free radicals and antioxidants, due to the excessive production of ROS and the reduction in the rate of its removal by the antioxidant defense system [7, 8].

Malondialdehyde (MDA) is an end-product derived from the peroxidation of polyunsaturated fatty acids and related esters. MDA does not just reflect lipid peroxidation but is also a byproduct of cyclooxygenase activity in platelets, and persistent platelet activation is a common feature of many clinical syndromes associated with enhanced lipid peroxidation [5]. MDA levels in total cancer patients and in both breast and lung cancer patients were significantly higher than those in healthy [9, 10].

Vitamin D is a fat-soluble vitamin that has two important roles in the body: (1) plays a role in the endocrine mechanism and plays a role in the autocrine /intracrine mechanism. The endocrine pathway involves a "classic" mechanism associated with increased calcium absorption in the intestine and osteoclast activity [11]. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis. Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH) vit D], also known as cholycaciferol. The second occurs primarily in the kidney and forms the physiologically active form of vitamin D which is the 1,25- $(OH)_2$ vitamin D [12, 13].

MATERIALS AND METHODS

This study investigated 90 women (60 patients and 30 controls), ages between (30-70) years. The patients were referred to three main facilities, Kirkuk oncology center, consultation of early detection of breast tumors in azady hospital, and Kirkuk general hospital from November 2022 to March 2023. The individuals of this study were divided into five groups: The first group was breast cancer women who have tumors in stage 1 and their n were (14). The second group was breast cancer women have tumors in stage 2 and their n was (22). The third group was breast cancer women who have tumors in stage 3 and their n were (16). The fourth group was breast cancer women who have a tumor in the metastatic stage and their n were (8). The fifth group was healthy women with a negative family history of breast cancer were included in this study as a control group. Clinical history data, information on age, weight, height, marital status, and family history of breast cancer. About 5 ml of venous blood was collected from each case by using a sterile disposable syringe then unloaded into gel tubes and allowed to clot at room temperature for 20 minutes. All samples were centrifuged at 3000 rpm for 15 minutes; sera removed and divided into three Eppendorf tubes 500 µl for each sample, then stored at - 30 C until used to the time of biochemical assay which included parameters: Malondialdehyde MDA. The kit was an Enzyme-Linked Immunosorbent Assay (ELISA) for all parameters which worked manually and then measured by the Mindry device. The work included the measurement of the weight and height of each woman included in this study and BMI was calculated by using the following formula: weight in kilograms divided by height in squared meters. Quantifying obesity by the BMI classification of WHO, and the international obesity task force.

RESULTS

The total number of a subject that participate were 90 (60 patients and 30 control). 16 (27%) within the age group of 35-44 years, followed by 24 (40%) within the ages group 45-55 years and 20(33%) within the ages 56-76 as seen in Table 1.

Table 1: Relation of breast cancer with age

Age group (years)	NO.	%
35-44	16	27
45-56	24	40
55-76	20	33
Total	**60**	**100%**

Our finding revealed a significant decline in serum vit D concentrations according to the control Group. The Coenzyme levels were (30.15±4.68) in women with breast cancer, and (47.79^{a}±7.40) in control group at p-value ($p < 0.009$), as shown in Table 2.

Table 2: Relation between breast cancer and healthy women regarding the mean ± SD of V i t. D

Studied groups	**V i t. D**
Breast Cancer women	30.15±4.68
Control Group	47.79±7.40
P. value	**0.009**

Estimation of serum MDA level in study groups

Our finding revealed a significant increase in serum MDA concentrations according to the control Group. The MDA levels were (5.561^{a}±0.582) in breast cancer women, and (2.727^{b}±0.414) in control group at p-value ($p < 0.00007$), as shown in Table 3.

Table 3: Relation between breast cancer and healthy women regarding the mean ± SD of MDA

Studied groups	**MDA**
Breast Cancer women	5.561 ± 0.582
Control Group	2.727 ± 0.414
P. value	**0.00007**

The mean serum V i t. D concentrations in women with breast cancer in stage I was (25.08^{b}±12.10), while in stage II(G2), stage III(G3), and stage IIII(G-M) were (27.68^{b}±23.39, 26.80^{b}±16.60, 18.97^{c}±14.35) respectively, in compared with control was (37.82^{a}±18.38) at p-value 0.040. The mean serum MDA in women with breast cancer in the stag I was (5.5020^{a}±0.7180), while in stage II(G2), stage III(G3), and stage IIII(G-M) were (5.9300^{a}±0.4636, 5.5800^{a}±0.6140, 5.4410^{a}±0.6350) respectively in compared with control was (2.6683^{b}±0.3487) at p-value 0.00009.

Table 4: Relation of MDA, and vit.D with the stage of breast cancer women

Breast cancer women	V i t . D	MDA
G1 (N.14)	25.08 ± 12.10	5.5020 ± 0.7180
G2 (N.22)	27.68 ± 23.39	5.9300 ± 0.4636
G3 (N.16)	26.80 ± 16.60	5.5800 ± 0.6140
G-M (N.8)	18.97 ± 14.35	5.4410 ± 0.6350
Control	37.82 ± 18.38	2.6683 ± 0.3487
P-Value	**0.040**	**0.00009**

This study found that there was a moderate positive correlation between MDA and vitD in women with breast cancer (R: 0.283), Figure (1).

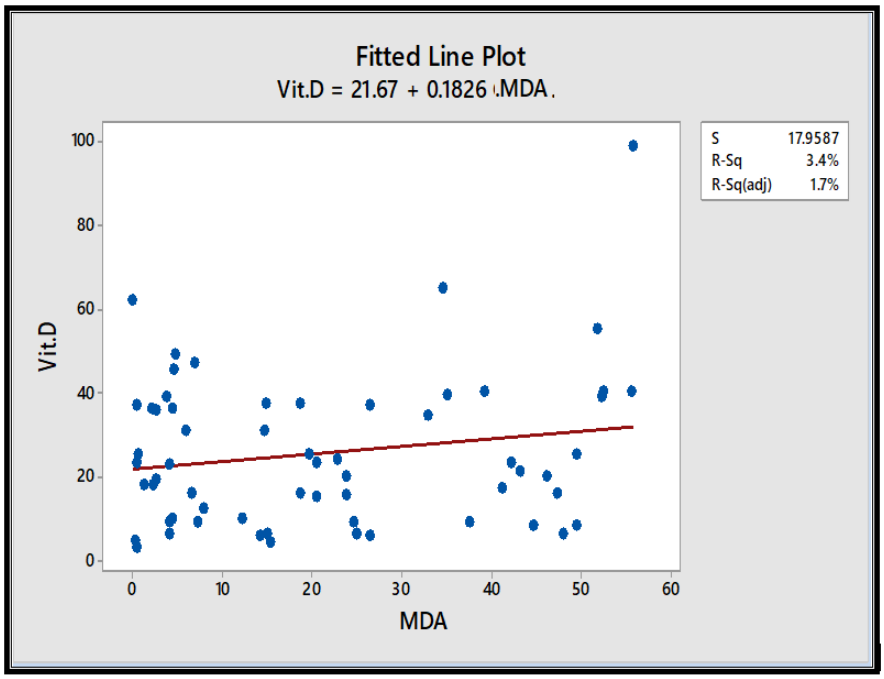

Figure 1: Correlation between MDA and vit D in breast Cancer Women

DISCUSSION

Our findings show an increase breast cancer incidence in age (45-56) and this agrees with [14] Khalil *et al.*, and [15] Heer *et al*., The maximum rate of the disease occurred in women above 48 years [16]. The incidence of cancers is closely related to the age group that was low in age 0-40 and increases rapidly with age increase due to obesity [17]. The incidence of breast cancer increasing with age that suggest may be due to DNA methylation which is one of the reasons behind increased BC with age, as it is a normal part of the aging process. Most essential reasons behind increased BC with age among Asians are poverty, poor dietary habits, and unhealthy lifestyle [18]. In the United Kingdom, where the age-standardized incidence of breast cancer among women aged between 50 to 60 years, maybe due to familial and hormonal factors [19]. Other studies show that the age-standardized incidence of breast cancer shows a steady rise from the adolescent period till it peaks at the 40–44-year age group. It starts declining but with a second lower peak at 46-50 years age group [20].

Also Among women with breast cancer diagnosed before age 45, a first-degree relative diagnosed with the disease under age 45 is an indicator of a mutation in BRCAl or BRCA2 even in the absence of a family history of breast cancer. Mutations in BRCA2 account for a substantial proportion of hereditary breast cancer [21].

The study showed that the mean of vitamin D was significantly lowered in breast cancer women as compared with the control group. Previous studies found that vitamin D deficiency had a negative effect on overall and disease-free survival in breast cancer cases, being related to tumor size, stage, grade, nodal status, and Her2/neu receptor expression [22]. The nutritional risk factors have gained considerable concern. Studies suggested that high fruit and vegetable intake with low saturated fats may reduce the risk of breast cancer [22]. Vitamin D is presumed to be one of such factors that can be modified to prevent breast cancer [23]. Another study found that the relation between vitamin D deficiency and poor outcome of BC seems to be critically affected by the timing of measurement of serum 25(OH)D levels. No significant association between 25(OH)D levels and BC recurrence or death was found in a study based on serum obtained approximately 2 years post-diagnosis on average [24]. Another studies found no association between post-treatment serum 25(OH) D and cancer-specific mortality after a relatively long follow up (median of 9.2 years) of 48 women with BC [25, 26].

In our finding show that the level of malondialdehyde result increase in breast cancer women significantly in compare with control groups at P-value 0.00007.Our result agree with Gönenç [27] and with Faber M [28]. MDA, one of the final decomposition products of lipid peroxidation, possess biological properties that may be relevant to carcinogenesis, and raised MDA levels in patients with breast cancer have provided further evidence of this relationship, and ultimately give rise about connection between lipid peroxidation and cancer [27]. MDA interact with functional groups of a variety of cellular compounds, including the amino groups of proteins and nucleic acid bases, the N bases of phospholipids and the SH groups of sulphydryl compounds that cause cancer promotion [29].

Oxidative stress and end products have been suggested to play a role in some physiological conditions and in many disease processes, including carcinogenesis that suggested that MDA as a marker of cancer progression [28]. Endogenous MDA formation and its mutagenicity suggested the possible role of this molecule in carcinogenesis. The potential of MDA in formation of DNA adducts and as a cofactor in formation of cathecolestrogen metabolites have been proposed for its role in estrogen-induced carcinogenesis plasma levels of cholesterol, triglyceride and a lipid peroxidation marker, MDA. Our findings disagree with [30] Zaridze *et al.,* and [31] Saintot *et al.,* plasma MDA levels were lower in breast cancer patients than in healthy controls. It has been suggested that high levels of polyunsaturated fatty acids and MDA in the erythrocyte membranes decrease the risk of breast cancer .Other study demonstrated that MDA can accumulate in human breast tissues and reach relatively high levels in the breast tissues of women with breast cancer, by mechanism, damage to the breast epithelium by chemical carcinogens as products of oxygen-free radical release can lead to fibroblast proliferation, hyperplasia of epithelium, cellular atypia, and breast cancer [32].

Our findings show a significant decrease in vit D in all stages of breast cancer, and more decrease in metastatic stage. This result agrees with Thangaraju [33]. Laboratory studies have demonstrated anticancer effects of vitamin D metabolites on three critical phases in the development of breast tumors: differentiation, apoptosis, and angiogenesis. It is possible that the association of serum 25(OH)D with survival depends on maintaining differentiation, promoting apoptosis, and inhibiting angiogenesis [34].

Higher serum 25(OH)D concentrations were associated with lower fatality rates in patients with breast cancer. Patients with the highest concentration of 25(OH)D had approximately half the fatality rate compared to those with the lowest concentration [35]. Palmieri [36] found that serum 25 (OH)D was significantly higher in patients in early-stage breast cancer compared to those with locally advanced disease. A negative correlation was observed by Hatse [37] between tumor size and lower serum 25(OH)D levels. Low circulating serum 25(OH)D concentrations were significantly associated with increased overall and disease-specific mortality. This association is further confirmed by another two studies concerning breast cancer patients [38] In addition, this active metabolite of vitamin D can potentiate the anticancer effects of many cytotoxic and antiproliferative anticancer agents [39].

Our findings agree with DO VAL [40]. Serum MDA found to be increased gradually from Stage I to Stage IV as compared to control group and the maximum rise was in Stage IV patient [41]. Oxidative stress resulting from an imbalance between pro-oxidants and anti-oxidants seems to play an important role in initiation, promotion and metastasis breast carcinogenesis [42]. Plasma MDA levels have been an indicator of lipid peroxidation in humans. Different results with regard to the levels of lipid peroxidation products, especially MDA, in various tumors including breast cancer [43].

Increased levels of lipid peroxidation products play a role in the early phases of tumor growth [44, 45]. Higher levels of oxidative stress, including increased MDA levels, in patients with various cancers have interpreted their data as the oxidative stress playing an important role in the process of carcinogenesis by means of inducing mutagenesis [46, 47]. One of the potential sources for plasma MDA is peripheral blood cells. The changes of white blood cells (WBC) and neutrophils could explain the variations of plasma MDA levels seen in breast cancer patients with early stages [48].

Other study Increased MDA levels after radiation has been shown to strengthen erythrocyte membranes by forming cross-connections with first amino groups of proteins or membrane phospholipids. The increase in MDA in cancer is linked to oxidative stress, which reduces polyunsaturated fatty acid (PUFA) in the plasma membrane, and causes mitochondrial malfunction [49]. Elevated MDA concentrations decreased with tamoxifen therapy in postmenopausal women with breast cancer [33].

CONCLUSION

Increased levels of lipid peroxidation products play a role in the early phases of tumor growth. Higher levels of oxidative stress, including increased MDA levels, in patients with various cancers have interpreted their data as oxidative stress playing an essential role in the process of carcinogenesis by means of inducing mutagenesis. One of the potential sources of plasma MDA is peripheral blood cells. The changes in white blood cells (WBC) and neutrophils could explain the variations of plasma MDA levels seen in breast cancer patients with early stages.

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