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Oxidative Stress Parameters in Patients with Breast Cancer before and after Radiotherapy

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REACTIVE oxygen species (ROS) are generated in response to endogenous or exogenous stimuli. Antioxidants defense system resists for balancing ROS-mediated injury; if oxidation exceeds the defense mechanisms, oxidative stress is generated. Oxidative stress may be involved in the development of breast cancer. Moreover, radiationtherapy (RT), used for the treatment of breast cancer, works by the production of reactive oxygen species at the site of radiation which leads to local oxidative stress. Studies which detect one or few oxidant and antioxidant markers failed to detect the overall oxidant/antioxidant status of the subjects. The authors aim at studying the impact of radiotherapy on the total oxidant status (TOS), total antioxidant status (TAS) with calculation of oxidative stress index (OSI), and measure the lipid peroxidation (MDA) in breast cancer patients.

TAS, TOS, MDA and OSI in healthy and breast cancer groups are measured. In breast cancer group, all parameters were measuredbefore and after radiation therapy.

In the breast cancer group, TOS, OSI and MDA levels have increased significantly ($P<0.001$) and the TAS level has decreased ($P<0.001$) in the breast cancer patients after radiotherapy than before radiotherapy. Breast cancer group TAS after RT reaches about forth its level measured inthe control group. Radiotherapy in breast cancer patients depletes the total antioxidants (TAS), increases total oxidative status (TOS), lipid peroxidation (MDA) and OSI. Breast cancer and its treatment modalities display the patients in a state of severe oxidative stress which requires the supplementation of antioxidants.

Keywords: Cancer breast, Radiotherapy, TOS, TAS, MDA.

Introduction

Cancer is the second cause of death worldwide and breast cancer is the most prevalent cancer in women, comprising 29% of all cancers affecting them as reported by Siegel et al. (2016). More than one million women are diagnosed with breast cancer annually as demonstrated by Zaleska (2015). The global incidence of breast cancer is increasing rapidly and in Egypt the incidence reaches 38% of cancers affecting females as shown by Ibrahim et al. (2014). A study by Feng et al. (2012) has reported that oxidative stress is related to the occurrence and development of breast cancer. The risk factors associated with breast cancer may exert their effects via generation of ROS, which induce oxidative damage of DNA, lipid peroxidation, neoplastic transformation and carcinogenesis. The formation of lipid peroxidation products is normally prevented or scavenged by host antioxidants as stated by Durackova (2010). Increase of oxidative stress can affect many cellular functions as cellular metabolism, intracellular signaling, gene regulation, proliferation, and apoptosis as reportedby Kim et al. (2013). Sheikhpour et al. (2018) concluded that excessive oxidative stress increases the incidence and progression of breast cancer, induces lipid peroxidation, increases

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inflammatory mediators, and it is involved in the inactivation of certain tumor suppressor genes. Radiotherapy, chemotherapy and hormone therapy are used for the treatment of breast cancer patients beside surgery, because of their ability to destroy remaining cancer cells after surgery (Murawa et al., 2014). Surgery, chemotherapy and radiotherapy procedures promote the generation of ROS via oxidative stress mechanism that can further worsen the state of tumor cells. Malik et al. (2018) demonstrated that low levels of enzymatic and non-enzymatic antioxidants, in patients with breast cancer which are further reduced after their surgical intervention and increase levels of oxidants in those patients, further increase after surgery. Radiation therapy depends on ROS toxicity which damages cellular macromolecules, such as DNA (deoxyribonucleic acid), RNA (ribonucleic acid), microRNAs, proteins and membrane of tumor cells as reported by Marín et al. (2015). Seifried et al. (2007) demonstrated that antioxidants protect normal cells against radiation injury by scavenging the free radicals through various enzymatic systems such as catalase, glutathione peroxidase and superoxide dismutase and non-enzymatic systems such as vitamin C, selenium, glutathione and vitamin E. Many studies had distinguished that malondialdehyde (MDA) concentration that represents lipid peroxidation has increased in breast cancer patients (Khanzode et al., 2004; Tas et al., 2005). However, another study reported that plasma MDA was decreased in breast cancer patients; and the decrease in plasma MDA was associated with the severity of tumor size in breast cancer patients (Gerber et al., 1997).

As some studies measure done or several individual oxidants/antioxidants in the serum, failed to consider the overall total oxidant status (TOS) which is used to estimate the overall oxidation state of the body (Erel, 2005). Similarly, the total antioxidant status (TAS) is used to measure the overall antioxidant status of the body (Erel, 2004). The oxidative stress index (OSI), which is the ratio of TOS to TAS (Aycicek & Erel, 2007), may be a more accurate index of oxidative stress in the body because it is a comprehensive measurement of TAS and TOS. The previous results of the effects of radiotherapy on various antioxidant/oxidant systems are inconclusive. Some studies have reported that radiotherapy is able to change the status of the antioxidant/oxidant system (Kasapović et al., 2010, Belwalkar et al., 2012), while others have foundthat radiotherapy hasno effect on the antioxidant/oxidant system (Khoshbin et al., 2015). Therefore, in the present study, to the authors aims at determining the exact effects of radiation therapy on malondialdehyde, total antioxidant status, total oxidant status, and oxidative stress index in breast cancer patients, and if these parameters change fromearly stages to advanced stages of breast cancer.

Patients and Methods

The study was conducted at Ain Shams University Hospital between February 2017 and December 2017. The study protocol was approved by the Research Ethical Committee of the NCRRT according to Helsinki declaration and consent was obtained from each patient prior to inclusion in this study. The present study includes 102 subjects, 32 were healthy women (control group) and 70 were women with breast cancer (patient group). The subjects were selected at different ages between 27-63 years. They were clinically and histopathologically diagnosed as malignant breast cancer within different stages. Patients included in this study were divided according to the disease stage to early stages group (I+II) and late stages group (III+IV) for comparison between different stages. The patients with gout, thyroid disease, osteoporosis, rheumatoid arthritis, pulmonary and liver diseases, were excluded to eliminate confounding variables. All personal and clinical data were collected upon recruitment. All the patients received surgical procedure, chemotherapy and radiotherapy. The chemotherapy regimens applied in treatment for those cancer breast patients were:

1. FEC x 3 then Tx4 in (57.1% of cases). FEC= 5-Fluorouracil (F), Epirubicin (E), Cytoxan (C). Repeat cycle every 3 weeks for 3 cycles, then followed by Paclitaxel (T). Repeat cycle every 3 weeks for 4 cycles.

2. FAC in (20% of cases) for 6cycles. FAC regimen received Fluorouracil (F), Cytoxan (C), Adriamycin(A). Repeat cycle every 3 weeks for 6 cycles.

3. AC x 4 then T x 4 in (22.9% of cases).

Radiation therapy to all the patients were at a dose of 50Gy divided to 20-25 sessions of radiation in the radiotherapy unit. Radiation was delivered by the Linear accelerator which delivers high

energy photon beam. Radiotherapy was with daily fractions of 2Gy on 5 consecutive days a week, and was applied to the chest wall including the surgical scar as well as internal mammary nodes. The chest wall and internal mammary lymph nodes were irradiated through two tangential fields, supraclavicular and axillary nodes were treated with a total dose of 50Gy.

Blood sampling: blood samples were collected from all patients twice (before starting the first session of RTand immediately after the end of last session of RT), and once from the control group. Blood samples were centrifuged at 3000rpm for 15min and serum samples were stored in aliquots at -70°C until analysis.

Measurement of TOS

Erle's method was used to measure serum TOS which was based on the oxidation of ferrous ion to ferric ion in the presence of various oxidative species under acidic conditions. The results were expressed in μmolH_2O_2 equivalent/L (μmolH_2O_2 equiv./L), (Erel, 2005).

Measurement of TAS

TAS was measured using the 2,2'-azino-di-3-ethylbenzthiazoline sulfonate $(ABTS)^+$ colorimetric method. This assay depends on the ability of antioxidants in the serum to inhibit the formation of $ABTS^+$ from the oxidation of ABTS by metmyoglobin (a peroxidase). The results were expressed in mmolTrolox equivalent/L (mmolTrolox equiv./L), (Erel, 2004).

Calculation of OSI

OSI was calculated using the following formula: OSI (arbitrary units)= [(TOS, μmolH_2O_2 equiv./L)/ (TAS, μmol Trolox equiv./L)× 100] (Aycicek & Erel, 2007).

Measurement of MDA

Lipid peroxidation, as the level of malondialdehyde (MDA), was analyzed using the thiobarbituric acid reactive substances (TBARS) assay. The principle of this assay is to determine lipid hydroperoxides levels by spectrophotometer, and the results were expressed in μmol/L, (Rael et al., 2004).

Statistical analysis

Analyses of the basic characteristics of the subjects were compared using the Student t-test. The results were expressed as the mean ± standard deviation. The different groups were compared using the independent-t-test, and one-way ANOVA. Comparisons were performed before and after treatment using paired-t-test. P values < 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS statistical software v20.0 (IBM).

Results

Table 1 shows that both positive estrogen receptors and progesterone receptors is present in 70% of patients. Histological type IDC is present in 92.9% of patients, Grade II is the most presented in the cells of the tumors (70%), and clinical stage II is the most presented stage in (40%) of patients followed by stage III.

TABLE 1. Characteristics and investigations of breast cancer in this study.

Mean ± SD	No.	(%)
Age (years) 45.12±8.96	70	100%
Family history		
Positive	11	15.7%
Negative	59	84.3%
Site		
Right	29	41.4%
Left	36	51.5%
Both	5	7.1%
Estrogen receptors		
Positive	49	70%
Negative	21	30%
Progesterone receptors		
Positive	49	70%
Negative	21	30%
HER-2		
Positive	27	38.6%
Negative	43	61.4%
Histology type		
IDC	65	92.9%
ILC	5	7.1%
Grade		
Grade I	10	14.3%
Grade II	49	70%
Grade III	11	15.7%
Clinical stage		
Stage I	15	21.4%
Stage II	28	40%
Stage III	21	30%
Stage IV	6	8.6%

HER-2: Human epidermal growth factor receptor, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma.

Table 2 shows the clinical characteristics and the treatment protocols which clarifies that modified radical mastectomy is performed in 57.1% of the patients, then breast conserving surgery in 34.3%. Surgery+ chemotherapy+ radiotherapy are the major regime of treatment in the patients. The treatment regime may start by chemotherapy for 4 cycles then surgical intervention, followed by chemotherapy then radiotherapy.

TABLE 2.Clinical characteristics in breast cancer patients in the present study.

TNM classification:	**No.**	**Percent**
T1	6	8.6%
T2	48	68.5%
T3	16	22.8%
N0	21	30%
N1	18	25.7%
N2	13	18.6%
N3	18	25.7%
M0	43	61.4%
M1	21	30%
M2	6	8.6%
Molecular diagnosis:		
HER 2 enriched	27	38.6%
Luminal	37	52.9%
Triple negative	6	8.6%
Surgery:		
BCS (Breast conserving surgery)	24	34.3%
MRM (Modified radical mastectomy)	40	57.1%
No	6	8.6%
Chemotherapy:		
FAC × 6	14	20%
AC× 4 then T×4	16	22.9%
FEC×3 then T×4	40	57.1%
Radiotherapy:		
Surgery+ chemo+ radiotherapy	64	91.4%
Chemo+ radiotherapy	6	8.6%
Hormonal:		
+ve hormonal treatment	49	70%
No hormonal treatment	21	30%

Radiotherapy was administrated in all patients (100%), and hormonal therapy was administrated to 70% of patients; Trastuzumab was administrated to 38.6% of the patients with positive HER2.

Table 3 shows that TAS level in the control group is (752.44± 242.19) µmol/L, in breast cancer group before radiotherapyis (326.13± 83.61) µmol/L, and is significantly reduced to (171.30± 37.17) µmol/L after radiotherapy.

Level of TOS in control group is 13.57± 2.89µmol/L which is significantly lower than that in breast cancer group(17.87± 2.58) µmol/L, which is further significantly increased after radiotherapy to (24.92± 3.41) µmol/L. As regards lipid peroxidation, MDA level in control group is (0.83± 0.21) µmol/L which is significantly lower compared to breast cancer group(2.83± 0.58) µmol/L and this level is increased significantly to (5.68± 0.911) µmol/L after radiotherapy. OSI is lowest in control group (0.19) and is significantly higher in breast cancer group before radiotherapy (0.59) and further increased after radiotherapy (1.52) which indicates the increase in oxidative stress by radiotherapy.

In Table 4 shows that the stages (I+II) of the breast cancer are considered as early G (n= 43) and stages (III+IV) of breast cancer as advanced stage G (n= 27). The effects of RT on the measured variables are compared in these two subgroups before and after RT. Serum level of TAS in early stage G (I+II) before radiotherapy is (313.95± 59.7) µmol/L, and in advanced stage G (III+IV) is (345.51± 110.2) µmol/L. Then the TAS level decreased significantly after radiotherapy to (169.81± 33.24) and (173.66± 43.28) µmol/L, respectively. TOS level of early stageG and advanced stageG are (17.46± 2.55, 18.52± 2.55) µmol/L before radiotherapy and are significantly increased after radiotherapy to (24.12± 2.58, 26.18± 3.50) µmol/L with significant higher level in advanced stage G. MDA level shows a significant increase in advanced stage G (3.33± 0.34) µmol/L than early stage G (2.51± 0.46) µmol/L, which further significantly increased after radiotherapy to (6.51± 0.52) and (5.16± 0.69) µmol/L, respectively. It is observed that MDA levels significantly increased inadvanced stage than early stage subgroups.

TABLE 3. Comparison between TAS, TOS, OSI and MDA in control group and in cancer breast patients group before and after radiotherapy using one-way ANOVA.

Parameter	Control group n= 32 (Mean± SD)	Patients group before RT n= 70 (Mean±SD)	Patients group after RT n= 70 (Mean+SD)	P
TAS µmol/L	752.44± 242.19	326.13± 83.61	171.30± 37.17	0.001
TOS µmol/L	13.57± 2.89	17.87± 2.58	24.92± 3.41	0.001
OSI	0.19	0.59	1.52	0.001
MDA µmol/L	0.83± 0.21	2.83± 0.58	5.68± 0،91	0.001

TABLE 4. Comparison between serum levels of oxidative stress parameters in patients with early stages cancer breast subgroup G (I+II) and late stages subgroup G (III+IV).

Parameter	Groups according to stages	N	Mean± SD	P
TAS before RT	Early G (I+II)	43	313.95± 59.70	0.125
	Advanced G (III+IV)	27	345.51± 110.26	
TAS after RT	Early G (I+II)	43	169.81± 33.24	0.676
	Advanced G (III+IV)	27	173.66± 43.28	
MDA before RT	Early G (I+II)	43	2.51± 0.46	0.001**
	Advanced G (III+IV)	27	3.33± 0.33	
MDA after RT	Early G (I+II)	43	5.16± 0.69	0.01*
	Advanced G (III+IV)	27	6.51± 0.51	
TOS before RT	Early G (I+II)	43	17.46± 2.54	0.095
	Advanced G (III+IV)	27	18.52± 2.55	
TOS after RT	Early G (I+II)	43	24.12± 3.50	0.05*
	Advanced G (III+IV)	27	26.18± 2.90	
OSI before RT	Early G (I+II)	43	0.58	0.70
	Advanced G (III+IV)	27	0.59	
OSI after RT	Early G (I+II)	43	1.45	0.06
	Advanced G (III+IV)	27	1.63	

Discussion

As radiotherapy depends on ROS production and toxicity, it is supposed that cancer treatment protocols of chemotherapy and radiotherapy induce oxidation, free radicals formation and at the same time reduce antioxidants. Antioxidants protect normal cells against radiation injury. In cancer patients there is disturbance in metabolism; when the patients are treated with chemotherapy then radiotherapy, they would experience another homeostasis disturbance which will affect the disease status. In this study, there is significant decrease in TAS level in the breast cancer

group compared to the control group before radiotherapy, which is significantly reduced again after radiotherapy. This is consistent with a research conducted by Zowczak-Drabarczyk et al. (2013) who reported that the plasma TAS significantly decreased in the breast cancer patients in comparison to the controls independently of hormonal and lymph node status.

In the present study, compared with the control group, TOS and MDA are significantly higher in breast cancer patients before RT. Further significant increases in these levels occur after radiotherapy. These results are consistent with that of Mehdi et al. who reported that the level of TAC of breast cancer patients wassignificantly lowerthan that of the healthy control group, while concentration of TOS among breast cancer patients were significantly higher than among the control group (Mehdi et al., 2018).

The effects of RT on the measured parameters were compared in the early stage (I+II) and advanced stage (III+IV) subgroups before and after RT. Serum level of TAS in early stage subgroup of breast cancer patients (I+II) before radiotherapy was (313.95± 59.7) µmol/L which was non significantly lower than in advanced stagegroup (III+IV) mean level (345.51± 110.2) µmol/L. Then the TAS level decreased significantly after radiotherapy to (169.81± 33.24) and (173.66± 43.28) µmol/L, respectively. Consistent with the currentresults, are those of Arjmandi et al. (2016) who found that the levels of TAS in early and advanced stages decreased significantly after radiotherapy. Before radiotherapy, the level of TOS in early and advanced stages groups were (17.46± 2.55) and (18.52± 2.55) which increased significantly after radiotherapy to (24.12± 2.58) and (26.18± 3.50) respectively; with a significant higher level in advanced stage group. Before radiotherapy the level of MDA shows a significant increase in advanced stage than early stages group, with further significant increases in MDA level after radiotherapy in advanced stages more than early stages which is in consistent with the study of Arjmandi et al. (2016) who reported that an increase in the level of MDA was observed in both stages of the disease after RT, but only in the early stage group, the difference was significant. The increase in the level of MDA and TOS in advanced group more than early group is perhaps due to excessive free radicals formation and lipid peroxidation occur due to the malignant tumor itself and due to chemotherapy given to the patients. It seems that antioxidant capacity, in patients with higher stages of the disease, is depleted after RT more than early stages and by time the several treatment modalities exhaust the antioxidant/oxidant system which cannot regulate homeostasis.

The presentresults are inconsistent with that of Zarrini et al. (2016) who reported that patients in advanced stages had lower serum TAS, but patients in the present study are similar to their study in having higher levels of MDA in advanced than early stages. Mean value of OSI in the control group is lower than the breast cancer group, and in early stages OSI is lower than advanced stages. This result is similar to that of Zarrini et al. who reported that within the different stages of breast cancer patients, OSI values were different as early stages had lower values than the advanced stages in breast cancer patients.

Feng et al. (2012), by screening the oxidative and anti-oxidative biomarkers in healthy subjects and patients with benign or malignant breast tumors, identified elevated serum TOS and OSI, while decreased TAS levels in both patient groups. The disruption of an overall antioxidant/oxidant balance in the patients suggests a potential link of oxidative stress to the pathogenesis of breast tissues. They measured severe antioxidant/oxidant disturbance in breast cancer patients more than benign breast tumor patients.

It seems that in the early stage of the disease, ROS formation would suddenly increase. After the disease progresses to higher stages, the body tries to compensate the occurring irregularities and the antioxidant enzymes, such as CAT, GPx and SOD, that are expressed more to overcome the overproduction of MDA in advanced stages, and this is observed in the present study, in which TAS in advanced stage group is insignificantly higher to compensate the higher levels of TOS and MDA.

Belwalkar et al. (2012) proved that MDA were elevated in patients before and after radiotherapy. SOD and vitamin E were low before and after radiotherapy. They hypothesized that radiation destroys tumor cells directly due to the excessive oxidative stress formed during radiation. Further reduced SOD and vitamin E after radiotherapy

interprets the utilization of existing antioxidant system for defending the additional oxidative stress. Huang et al. (2017) measured serum TOS, TAS, and OSI in patients with esophageal cancer and healthy controls and were all significantly different, but they found no significant differences across different clinical stages in the cancer group.

Wu et al. showed that serum oxidative stress parameters (TOS, TAS, and OSI) are correlated with the stages of colorectal cancer, and they suggest that oxidative stress parameters might indicate the severity of colorectal cancer (Wu et al., 2017).

Thanoon et al. (2013) in their study found that lipid peroxidation MDA increased in breast cancer women, while TAS level decreased. After surgery of breast cancer they noticed decreased lipid peroxidation with an increase of antioxidant defense system. They suggested that lipid peroxidation may be a consequence of cancer disease. Then patients after chemotherapy had again increased MDA and depressed antioxidant defense system TAS.

An explanation for the lack in antioxidant status before radiotherapy treatment may be that the patients are depleted of antioxidants because the cancer cells them selves increase oxidative stress and chemotherapy add to the oxidative stresswith the result of depleting circulating plasma antioxidants.

A meta-analysis suggested that post-diagnosis cancer breast vitamin C antioxidant supplementation may be associated with a reduced risk of mortality. Dietary vitamin C intake was also statistically associated with a reduced risk of total mortality and breast cancer-specific mortality (Harris et al., 2014). The complexity and genetic heterogeneity of advanced breast cancer suggest that the focus of cancer prevention efforts should be on the early interruption of the carcinogenic process (Meyskens et al., 2016).

Genetic instability due to persistent oxidative stress will increase the malignant potential of the tumor cells. Therefore, it is suggested that breast cancer patients should consider a specific attention in nutritional and antioxidant supplementation. Alleviating oxidative stress, using antioxidants, and physical activity were suggested as preventive strategies for breast cancer initiation and progression, as increased level of antioxidants is probably able to decrease the rate of normal cell transformation to malignancy (Coughlin, 2018).

Conclusion

Radiotherapy has doubled TOS, MDA levels, and OSI is tripled than before RT, and reduced TAS level to the half. Compared with controls, serum TAS of breast cancer patients is significantly lower, which further decreased after RT. TOS, OSI and MDA are significantly higher in breast cancer patients compared with the controls, with further increases occur after radiotherapy.Antioxidants should be used after radiotherapy to breast cancer patients to prevent the activation of another carcinogenic process.

Conflict of Interest: The authors declare no conflict of interest.

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منظومة الإجهاد التأكسدى فى المريضات بسرطان الثدى قبل وبعد العلاج الإشعاعي

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لا يعلم أحد ما هي مسببات سرطان الثدي، ولا توجد طريقة لنمنع الإصابة به حتى الآن. ويشكل سرطان الثدي ثلث حالات السرطان بين النساء، كما يعتبر أكثر أنواع السرطان شيوعًا بين السيدات. من الدراسات السابقة يتبين أن المركبات الناتجة عن الأكسدة يزداد بعضها مع العلاج المصاحب لسرطان الثدى والمواد التى تعتبر مضادات الأكسدة تقل بنسب متفاوتة.

تم اجراء ابحاث سابقة بقياس مركبات الأكسدة ومضادات الأكسدة كل على حدة، لذلك صممت هذه الدراسة لتقييم منظومة الأكسدة الكلية ومنظومة مضادات الأكسدة الكلية مع قياس المالونديالدهايد في النساءالمصابات بسرطان الثدي قبل وبعد العلاج الكيميائى والإشعاعى.

لذلك صممت هذه الدراسة لتقييم منظومة الأكسدة الكلية ومنظومة مضادات الأكسدة الكلية في النساءالمصابات بسرطان الثدي قبل وبعد العلاج الإشعاعى.

أجريت هذه الدراسة في مستشفى عين شمس على أربعين امرأة مصابات بسرطان الثدي تشكل المجموعة الأولى والمجموعة الضابطة مكونة من عشرين من النساء الأصحاء. أخذت عينات الدم (5 ملم) من المريضات والمجوعة الضابطة وتم قياس تركيز مالونديالدهايد فى مصل الدم وتركيز منظومة الاكسدة الكلية ومضادات الأكسدة الكلية في مصل الدم. أخذت عينات الدم قبل وبعد العلاج الأشعاعى. وكانت الجرعة العلاجية الإشعاعية 50 جراى مقسمة على 5 ايام اسبوعيا لمدة 5 اسابيع.

كان تركيز مالونديالدهايد و منظومة الاكسدة الكلية فى مصل الدم في المريضات المصابات بسرطان الثدي أعلى معنويا ($p< 0,001$) فيما انخفض تركيز مضادات الأكسدة الكلي معنويا ($p< 0,001$) بالمقارنة بالمجموعة الضابطة. وبعد العلاج ارتفع مالونديالدهايد فى مصل الدم معنويا ($p< 0,001$) وانخفض مضادات الأكسدة الكلي معنويا مقارنة بالنتائج قبل العلاج. آما أن العلاج السرطاني سبب ارتفاع معنوي ($p< 0,001$) فى مالونديهايد مصل الدم مصاحبا بانخفاض معنوي ($p< 0,001$) في تركيز مضادات الأكسدة مقارنة مع المريضات قبل وبعد العلاج وكذلك مقارنة مع المجموعة الضابطة.

ازداد تركيز منظومة الاكسدة الكلية في المريضات المصابات بسرطان الثدي بينما انخفضت منظومة مضادات الأكسدة. وخلصت الدراسة أن العلاج المضاد للسرطان يرفع من منظومة الأكسدة الكلية ويقلل من منظومة مضادات الأكسدة الدفاعية.