Evaluation of Oxidative Stress Involvement in Breast Cancer Carcinogenesis

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This work was carried out in collaboration among all authors. Author MES, work idea, practical work and manuscript final revision. Author AESAM, manuscript final revision. Author HEM, manuscript final revision. Author OF, patients selection criteria and final revision. Author SR patients samples and data collection and final revision; and author SMH statistical analysis, manuscript editing, review and submission. All authors read and approved the final manuscript.

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ABSTRACT

Background: According to GLOBOCAN estimates, breast cancer was found to be the most often diagnosed cancer in women worldwide, (11.7%) and the fourth leading cause of cancer mortality (6.9%). The present study was aimed to evaluate the involvement of oxidative stress on breast cancer carcinogenesis in Egyptian population.

Methods: Lipid peroxidation as evidenced by malondialdehyde (MDA) and nitric oxide (NO) stress as well as the status of the antioxidants superoxide dismutase (SOD) and total antioxidant capacity (TAC) were estimated in serum of 163 breast cancer patients. Correlations between oxidative/antioxidant profile and different prognostic variables in BC patients were estimated.

Results: Lipid peroxidation in BC was enhanced in response to cancer stage and tumor size (p < 0.01). Similarly, NO was increase in response to NPI, Her2/neu and cancer stage (p < 0.02). Inversely in antioxidant, SOD was decrease in response to Her2/neu only (p < 0.002). While, TAC

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was increase in response to cancer stage and tumor size (p < 0.01). We found that oxidative/antioxidant status was dependent on NPI, Her2/neu, cancer stage and tumor size of BC patients.

**Conclusion:** Higher oxidative stress generation and lower SOD activity were found in our study, which supports the oxidative stress concept in breast carcinogenesis.

**Keywords:** Breast cancer; oxidative stress; antioxidant; carcinogenesis.

**ABBREVIATIONS**

- **BC**: Breast Cancer,
- **Her2**: Human Epidermal Growth Factor Receptor 2,
- **ER**: Estrogen Receptor,
- **PR**: Progesterone Receptor,
- **IRB**: Institutional Review Board,
- **NPI**: The Nottingham Prognostic Index,
- **MDA**: Malondialdehyde,
- **NO**: Nitric Oxide,
- **SOD**: Superoxide Dismutase,
- **TAC**: Total Antioxidant Capacity,
- **ROS**: Reactive Oxygen Species,
- **RNS**: Reactive Nitrogen Species,
- **NCI**: National Cancer Institute,
- **REDOX**: Reduction-oxidation,
- **ROC**: Receiver Operating Characteristic Curve,
- **AUC**: Area Under Each Curve.

**1. INTRODUCTION**

Breast cancer (BC), consider the persistent diagnosing type of cancer worldwide which growing with more than two million new cases each year reflecting over (11.7%) of all lived diagnosed cancer. It is the leading cause of death in women, accounting for more than 6.9% of all cancer fatalities. Female BC death rates were higher in transitioning nations (15.0 to 12.8 per 100,000 cases) than in transitioned countries [1]. Breast cancer is the most common cancer among Egyptian women, accounting for more than (32%), with a three-fold increase expected by 2050, according to the National Cancer Institute (NCI) of Egypt [2]. Egypt has a lower incidence of BC than the United States and other Western cultures, but Egyptian BC patients have a higher fatality rate. In Egyptian women, BC is the second largest cause of cancer death. Patients with no family history of BC account for 85 percent of all diagnosed BC in Egypt. This may explained by the genetic mutations that happen as a result of the aging or life style with a tendency to occur in younger age groups with advanced stages [3-5].
role in DNA damage in breast cancer, which can suppress or increase transcription, signal transduction pathways, replication mistakes, genomic instability, and oncogene activation. Several risk factors for breast cancer are linked to ROS-induction, including ageing, menopause, genetic susceptibility, and estrogens, all of which cause DNA damage and chromosomal abnormalities, promoting the disease's growth and spread. Targeting REDOX regulation is emerging as a viable technique for the treatment of breast cancer [10,12,13,17], given that the management of oxidative stress and the preservation of REDOX homeostasis are critical determinants in both tumour development and response to anticancer therapy.

We therefore try to evaluate the extent of lipid oxidative, peroxidation (MDA) and nitric oxide (NO) as well as the status of the antioxidants superoxide dismutase (SOD) and total antioxidant capacity (TAC) in the involvement of breast cancer carcinogenesis.

2. MATERIALS AND METHODS

2.1 Patients Recruited

BC female patients 163 the median age = 52.7 years, (age range = 27– 80 years). BC patients are classified by different grading systems which influence the prognosis and different factors for histopathological diagnosis. Histological appearance is usually used to classify BC which is derived from the lobules or epithelium lining the ducts and these cancers are classified according grade, stage, node status and metastasis as well operation type [18]. Tumor size, as well as ER, PR, and Her2 statuses, were determined for each patient, and the BC group was then able to link these individual prognostic variables to the ACE I/D polymorphism genotypes. Patients in the BC group have recently been diagnosed with breast cancer and have not had any chemo/radiotherapy. Each BC patient's NPI, or Nottingham prognostic index, which accurately predicts survival in BC patients [19], was calculated. Three prognostic groups were separated by cut-off points. They were (NPI of < 3.4) represent the good prognostic index (GPI), (NPI of 3.41–5.4) was performed as the moderate prognostic index (MPI) and finally the (NPI of > 5.41) were illustrating the poor prognostic index (PPI). The equation used in NPI quantitation is:

\[ \text{NPI} = (0.2 \times \text{tumor size}) + \text{Node status} + \text{Grade status}. \]

2.2 Determination of Oxidative/Antioxidant Status

Plain tubes were used to collect blood samples. Serum was collected after spin at 2500 g for 9 min at RT. Oxidative/Antioxidant parameters (MDA, NO, SOD and TAC) were done according to the instructions of the manufacture (Bio-diagnostic, Giza, Egypt).

2.3.1 Lipid peroxide (Malondialdehyde, nmol / ml) Cat. No. MD 25 29

Thiobarbituric acid (TBA) reacts with malondialdehyde (MDA) in acidic medium at temperature of 95°C for 30 min to form thiobarbituric acid reactive product the absorbance of the resultant pink product can be measured at 534 nm.

2.3.2 Nitric oxide assay (NO, μmol/ L) Cat. No. NO 25 33

In acid medium and in the presence of nitrite the formed nitrous acid diazotise sulphanilamide and the product is coupled with N-(1–naphthyl) ethylenediamine. The resulting azo dye has a bright reddish – purple color which can be measured at 540 nm. It depend on the addition of Griess Reagents which convert nitrite into a deep purple azo compound, photometric measurement of the absorbance due to this azo-chromophore accurately determines NO2 - concentration.

2.3.3 Superoxide dismutase (SOD, U/ ml) Cat. No. SD 25 21

This assay relies on the ability of the enzyme to inhibit the phenazine methosulphate-mediated reduction of nitroblue- tetrazolium dye. The amount of SOD present in cellular and extracellular environments is crucial for the prevention of diseases linked to oxidative stress. Measure the increase in absorbance at 560 nm. The amount of SOD present in cellular and extracellular environments is crucial for the prevention of diseases linked to oxidative stress.

2.3.4 Total antioxidant capacity (TAC, mM/ L) Cat. No. TA 25 13

The determination of the anti-oxidative capacity is performed by the reaction of antioxidants in the sample with a defined amount of exogenously provide hydrogen peroxide (H2O2). The antioxidants in the sample eliminate a certain amount of the provided hydrogen peroxide. The residual H2O2 is determined calorimetrically by an enzymatic reaction which involves the
conversion of 3, 5, dichloro–2–hydroxy benzene sulphonate to a colored product. The absorbance of the resultant product can be measured at 505 nm.

2.4 Statistical Analysis

Frequency tables and statistical analyses were calculated with SPSS for Windows 21.0 (SPSS, Chicago, IL, USA). The data for analyses are expressed as mean SEM. Statistical comparisons were performed by Student’s t-test. Pearson correlation test was used in correlation between all parameters. A value of p <0.05 was considered statistically significant.

3. RESULTS

3.1 Demographic, Distribution of Prognostic Parameters BC Patients

The demographic, clinicopathological, and biomarker parameters of research participants were acquired from patients’ medical records and displayed in the graph (Table 1). The number and proportion of each metric in relation to BC patients are represented by the various attributes provided in the table. Among these features the predominant cancer stage was stage II (67.5%), node status was N0 (34.4%), cancer grade was grade II (71.2%), tumor size was ≥ 2 cm- 5 cm (74.2%), NPI was >3.4- 5.4 (76.7%), positive ER was (79.8%), positive PR was (76.1%), negative Her2/neu expression was (54.6%), negative metastasis was (85.3%) and left operated breast was (61.3%).

3.2 Correlation of NPI with Prognostic Parameters in BC Patients

Regarding NPI, the correlation among different prognostic parameters in BC patients was listed in (Table 2). The significant increase in NPI has been noted in positive Her2/neu expression marker (p= 0.05) as well as positive metastasis (p= 0.01) when compared to the negative ones. NPI also show a significant increase as the cancer stage and tumor size increase (p< 0.0001). NPI show no significant differences in response to neither ER nor PR.

3.3 Correlations of Oxidative/ Antioxidant Profile to Different Prognostic Parameters in BC Patients

The correlations between oxidative/antioxidant profile (Mean ± SEM) and different prognostic parameters in breast cancer are presented in Table 3. MDA shows a significant increase as the cancer stage and tumor size increase (p = 0.01, 0.05 respectively). NO shows a significant increase as the NPI and cancer stage increase (p= 0.04, 0.02 respectively) as well as positive Her2/neu expression marker (p= 0.02). SOD shows a significant decrease in positive Her2/neu expression marker (p= 0.002). TAC shows a significant increase as the cancer stage and tumor size increase (p= 0.01).

3.4 The Interrelationships of Oxidative/Antioxidant Status in Response to NPI, Oxidative Stress and Antioxidant in BC Patients

The interrelationships of oxidative/antioxidant status in response to NPI (Table 4), oxidative stress (Table 5) and antioxidant (Table 6) were calculated using Pearson correlation test. We determined similar data existed in literature.

3.5 Diagnostic Performance of Serum Oxidative/Antioxidant Status to Different Prognostic Parameters in BC patients:

Fig. 1, depicts the results of the ROC curve analysis which was used to explore the discrimination ability of serum oxidative/antioxidant status with response to different prognostic parameters in BC patients. Case Processing Summary revealed that larger values of the test result variable(s) indicate stronger evidence for a positive actual state. The test result variable(s): MDA, NO, SOD, TAC and NPI have at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. Table 7, presents the values of area under the curve of serum levels of MDA, NO, SOD, TAC and calculated NPI as well as Sensitivity and Specificity using ROC curve in response to different prognostic markers. The significant AUC was a result of data analysis of the ROC curve in response to Her2/new (AUC = 0.398, p = 0.02 for NO; AUC = 0. 619, p = 0.009 for SOD and AUC = 0. 412, p= 0.05 for NPI). The rest of markers give no significant difference in the AUC except in metastasis with NPI where it was (AUC = 0.347, p= 0.01). SOD shows the highest sensitivity and specificity over 90% in response to different prognostic markers.
Table 1. Characteristic frequency of tumor different prognostic factors in BC patients (163 Patients)

| Variables          | Patients # (%) | Variables          | Patients # (%) |
|--------------------|----------------|--------------------|----------------|
| Cancer Stage       |                | Node Status        |                |
| T1                 | 26 (15.9)      | N0                 | 56 (34.4)      |
| T2                 | 110 (67.5)     | N1                 | 42 (25.7)      |
| T3                 | 21 (12.9)      | N2                 | 40 (24.5)      |
| T4                 | 6 (3.7)        | N3                 | 25 (15.4)      |
| Overall grade      |                | Tumor size         |                |
| G1                 | 3 (1.8)        | <2cm               | 14 (8.6)       |
| G2                 | 116 (71.2)     | 2-5cm              | 121 (74.2)     |
| G3                 | 44 (27)        | >5 cm              | 28 (17.2)      |
| NPI                |                | Operation Type     |                |
| >2.4-3.4           | 5 (3.1)        | Lt MRM             | 100 (61.3)     |
| >3.4-5.4           | 125 (76.7)     | Rt MRM             | 63 (38.7)      |
| >5.4               | 33 (20.2)      |                    |                |
| ER                 |                | PR                 |                |
| Negative           | 33 (20.2)      | Negative           | 39 (23.9)      |
| Positive           | 130 (79.8)     | Positive           | 124 (76.1)     |
| Her2/neu           |                | Metastasis         |                |
| Negative           | 89 (54.6)      | Negative           | 139 (85.3)     |
| Positive           | 74 (45.4)      | Positive           | 24 (14.7)      |

Table 2. Correlations between NPI and different prognostic factors in BC patients.

| Variables    | Mean ± SEM | P   | Variables    | Mean ± SEM | P   |
|--------------|------------|-----|--------------|------------|-----|
| Her2/neu     |            |     | Metastasis   |            |     |
| Negative     | 4.57 ± 0.08| 0.052 | Negative     | 4.62       |     |
| Positive     | 4.82 ± 0.09| 0.052 | Positive     | 5.07       | 0.012 |
| ER           |            |     |              |            |     |
| Negative     | 4.61 ± 0.14| 0.052 | Negative     | 4.77 ± 0.14| 0.046 |
| Positive     | 4.71 ± 0.07| 0.052 | Positive     | 4.66 ± 0.07| 0.47  |
| Cancer Stage |            |     | Tumor size   |            |     |
| T1           | 4.05 ± 0.12|       | <2cm         | 4.10 ± 0.19|     |
| T2           | 4.66 ± 0.07| 0.000 | 2-5cm        | 4.62 ± 0.07| 0.01  |
| T3           | 5.34 ± 0.13| 0.000 | >5 cm        | 5.29 ± 0.14| 0.000 |
| P1           | T2 VS T3   | 0.000 | P1           | 2cm-5cm VS | 0.000 |

Table 3. Correlations between oxidative / antioxidant profile and different prognostic factors in BC patients

| Variables    | MDA          | NO            | SOD           | TAC           |
|--------------|--------------|---------------|---------------|---------------|
| NPI          | Mean ± SE    |               |               |               |
| 3.4-5.4      | 10.67 ± 0.82 | 12.68 ± 1.06  | 10.22 ± 0.26  | 3.33 ± 0.34   |
| >5.4         | 10.78 ± 1.84 | 17.49 ± 2.09  | 11.11 ± 0.49  | 2.73 ± 0.83   |
| P            | 0.95         | 0.04          | 0.11          | 0.45          |
| Her2/neu     |              |               |               |               |
| Negative     | 10.25 ± 1.03 | 11.63 ± 1.22  | 11.02 ± 0.29  | 3.51 ± 0.5    |
| Positive     | 11.32 ± 1.09 | 15.79 ± 1.40  | 9.58 ± 0.34   | 2.86 ± 0.36   |
| P            | 0.47         | 0.02          | 0.002         | 0.296         |
| Cancer Stage |              |               |               |               |
| T1           | 9.25 ± 1.69  | 12.60 ± 2.32  | 10.53 ± 0.52  | 2.99 ± 0.67   |
| T2           | 10.16 ± 0.83 | 13.32 ± 1.14  | 10.45 ± 0.28  | 2.92 ± 0.31   |
| T3           | 15.99 ± 2.91 | 16.82 ± 2.71  | 9.39 ± 0.74   | 5.20 ± 1.65   |
| (T1<T2) P    | 0.63         | 0.78          | 0.90          | 0.92          |
### Table 4. Correlations between oxidative and antioxidant in response to NPI prognostic value in BC patients

| Oxidant/Antioxidant | NO | SOD | TAC |
|---------------------|----|-----|-----|
| MDA                 |    |     |     |
| Correlation         | -.110| -.281| .547|
| Sig. (2-tailed)     | .165| .000| .000|
| NO                  |    |     |     |
| Correlation         | -.267| -.255|    |
| Sig. (2-tailed)     | .001| .000|    |
| SOD                 |    |     |     |
| Correlation         | -.022|    |    |
| Sig. (2-tailed)     | .785|    |    |

### Table 5. Correlations between oxidative and antioxidants in response to oxidative stress (MDA and NO) in BC patients

| MDA | SOD | TAC | NO | Oxidant/Antioxidant | SOD | TAC | MDA |
|-----|-----|-----|----|---------------------|-----|-----|-----|
| .104| .009| .138| NPI| Correlation         | .136| .050| .026|
| .190| .909| .080|    | Sig. (2-tailed)     | .084| .531| .746|
| .165| .293| .000| SOD| Correlation         | -.088| -.317| .000|
| .036| .000| .263|    | Sig. (2-tailed)     | .264| .541| .000|
|     | .003| .264| TAC| Correlation         | .541| .000|    |
|     |     | .001|    | Sig. (2-tailed)     | .000|    |    |

### Table 6. Correlations between oxidative and antioxidants in response to Antioxidants (SOD and TAC) in BC patients

| MDA | NO | TAC | Oxidant/Antioxidant | MDA | NO | SOD |
|-----|----|-----|---------------------|-----|----|-----|
| .039| .166| .015| NPI                 | .004| .144| .097|
| .620| .034| .846|                    | .960| .067| .221|
| .190| .564| .015| MDA                 | .037| -.320| .000|
| .015| .000| .264|                    | .640| .000|    |
|     | .001| .263| NO                  |     | -.263| .001|
|     |     |     | Sig. (2-tailed)     |     | .000|    |
Fig. 1. ROC curve for Oxidative and Antioxidants in response to different prognostic markers in Breast Cancer Patients.

Table 7. AUC, Sensitivity and Specificity of Oxidative and Antioxidants parameters in response to different prognostic factors in BC patients using ROC curve

| Parameters | Sensitivity % | Specificity % | AUC  | CI 95%     | P      |
|------------|---------------|---------------|------|------------|--------|
| MDA        |               |               |      |            |        |
| ER         | 60.8          | 57.6          | 0.532| 0.420-0.643| 0.576  |
| PR         | 67.7          | 69.2          | 0.479| 0.381-0.578| 0.694  |
| Her2       | 56.8          | 50.6          | 0.554| 0.466-0.643| 0.235  |
| Met.       | 62.5          | 71.9          | 0.460| 0.332-0.588| 0.535  |
| NO         |               |               |      |            |        |
| ER         | 63.8          | 57.8          | 0.469| 0.365-0.574| 0.587  |
| PR         | 85.8          | 89.7          | 0.463| 0.360-0.567| 0.491  |
| Her2       | 86.5          | 80.9          | 0.602| 0.514-0.689| 0.026  |
| Met.       | 91.7          | 84.2          | 0.536| 0.425-0.646| 0.577  |
| SOD        |               |               |      |            |        |
| ER         | 94.6          | 90.9          | 0.525| 0.415-0.635| 0.663  |
| PR         | 92.7          | 87.2          | 0.568| 0.468-0.668| 0.202  |
| Her2       | 91.9          | 98.9          | 0.381| 0.295-0.467| 0.009  |
| Met.       | 100           | 89.9          | 0.582| 0.470-0.693| 0.203  |
| TAC        |               |               |      |            |        |
| ER         | 86.9          | 81.8          | 0.505| 0.393-0.617| 0.931  |
| PR         | 87.1          | 82.1          | 0.541| 0.438-0.644| 0.438  |
| Her2       | 85.1          | 89.9          | 0.463| 0.373-0.552| 0.413  |
| Met.       | 79.2          | 90.6          | 0.409| 0.285-0.533| 0.155  |

AUC = Area under the ROC curve, CI=Confidence Interval, P=Significance level
4. DISCUSSION

Breast cancer is a complex and multifaceted disease in which environmental and genetic variables combine to cause the disease's origin and progression. Breast cancer is now well recognised as the most often diagnosed cancer in women worldwide and a leading cause of cancer mortality in women [1]. The spread of BC in Egypt is increasing, and it remains a major health issue in the country with no remedy. It accounts for 33% of all female cancer cases, with about 22,000 new cases identified each year [20]. Given the growing population, this is anticipated to increase enormously in the next years. According to the National Cancer Institute (NCI), Egypt [2] a three-fold rise is expected by 2050. Thus, it requires improved methods of screening, diagnosis, and treatment. In this disease, risk factors are multifactorial including obesity, delayed menopause, history of benign breast disease, genetics, and early menarche. These factors compromise all cellular mechanisms including cell proliferation, pathways of gene expression regulation, and apoptosis [21,22].

In the present study, the Nottingham Prognostic Index NPI, was calculated to each case and correlated to different prognostic parameters in BC patients [8], where it shows significant increase in positive Her2/neu expression as well as positive metastasis ones. NPI also show a significant increase as the cancer stage and tumor size and no change in response to neither ER nor PR. It seems that we are the first to correlate this index to different prognostic parameters in BC patients.

A state of imbalance between pro-oxidant and antioxidant is referred to as oxidative stress. An enzymatic and non-enzymatic antioxidant defence mechanism neutralises oxidants under normal physiological settings. Antioxidants will not be able to completely remove free radicals, resulting in a buildup of reactive oxygen species (ROS) [11–13]. Some research [23-25] found greater serum MDA levels in breast cancer patients, whereas others found lower levels [22,26]. Our findings backed up the widely held belief that breast cancer is associated with a higher level of MDA than healthy people (data not shown). Because our patients were recently diagnosed breast cancer patients, the elevated level of oxidative agents could be a sign of cancer progression in its early stages. Increased MDA level in the serum of breast carcinoma was found to be significantly increased with the increase of tumor stage and tumor size. In this study, NO shows also significant increased with the increase of tumor stage and tumor size as well as predictive index NPI increase and with positive Her2/ neu expression.

The increase in serum lipid peroxidation in breast cancer seen in the present study was associated with enhanced antioxidant capacities. Increased generation of oxygen free radicals can induce TAC but not SOD, in concomitant to our findings, Gupta et al., [21] shows decreased SOD activity in breast cancer patients. An increase in SOD activities due to overexpression has been reported [23]. In our study, SOD activities were found significantly lower in positive Her2/ neu expressed patients and not changed in response to other predictive markers, while the activity of TAC is significantly increased with the increase of tumor stage and tumor size.

Our finding showed that serum level of MDA was positively linked with the NO, SOD and TAC but not with NPI. Our findings could support the potential diagnostic value of MDA and NO in BC. To the best of our knowledge, this is the first study to report the sensitivity and specificity for MDA, NO, SOD and TAC in response to different prognostic factors in BC patients; previous studies focused only on one or few oxidative/antioxidant biomarkers to evaluate oxidative stress status in BC [22,23]. Despite supporting the association of the studied biomarkers with the occurrence and progression of BC, these reports were insufficient to reflect the true status of oxidative stress in those patients or reveal the potential clinical value of the studied biomarkers for the diagnosis or prediction of BC. Moreover, the studied panel of oxidative/antioxidant biomarkers may potentiate each other in amplifying their biological effects [23]. Expected mechanisms for the increase of oxidative stress in breast cancer were supposed to induce genetic changes in antioxidant enzymes, estrogen treatment, increase of reactive oxygen species generation, as well as decrease in antioxidant system [27]. There are considerable facts documented the effects of free radicals, oxidative damage, and lipid peroxidation in initiation and development of cancer types such as breast cancer. The best method to evaluate oxidative stress is to measure the compounds obtained by the reaction of oxidants with biomolecules as a biomarker which is clinically important in evaluation and identifying cancers [10,21,27,28].
The analysis of the receiver operating characteristic curve (ROC) for oxidative/antioxidant was plotted and the area under each curve (AUC) was calculated. A better diagnostic value has been detected when the area under the ROC curve is large. Derouiche et al., [22] used the ROC curve to evaluate the diagnostic value of MDA, GSH and catalase for breast cancer. This study showed that oxidative stress markers NO and SOD in serum, have a significant correlation with breast cancer marker Her2/neu expression, which can serve as a sensitive indicator of a cancer diagnosis. The high sensitivity and specificity of NO and SOD in serum is a very sensitive marker to oxidative stress. In the current study, ROC curve analysis of oxidative/antioxidant revealed that SOD and NO have potential diagnostic value in BC patients, where it shows a highly sensitivity and specificity. Previously, the performance characteristics of other oxidative stress biomarkers revealed that oxidative stress had a better BC diagnostic value than total antioxidant status [29].

5. CONCLUSION

In conclusion, the findings of the present study show that patients with breast cancer are more exposed to oxidative stress with higher free radical production increased oxidative stress as evidenced by an increase in oxidative markers MDA and NO and a decrease in antioxidant marker SOD. This oxidative stress is related to Her2/neu expression marker of breast cancer. This study is confirming the importance of preventing oxidative stress to prevent the development/progression of breast cancer where oxidative stress plays an important role. Further understanding of tumor biology from the standpoint of reactive oxygen species may be helpful for establishing a new strategy for cancer therapy.

CONSENT AND ETHICAL DECLARATION

The patients were admitted to Mansoura University Oncology Center Hospitals, Mansoura, Egypt, over the years 2019 and 2020. The protocol approval was allowed by the Institutional Review Board (IRB) at Mansoura University before starting the study. All methods were performed in accordance to the guidelines and regulations proposed in the 1975 Declaration of Helsinki. Informed consent letter was obtained from all the participants. All the patient related data including biological samples were anonymized to ensure confidentiality.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;0:1-41. DOI: 10.3322/caac.21660
2. National Cancer Institute, Cairo University. Available: http://www.nci.cu.edu.eg/. Accessed 10 Nov 2020.
3. Feng Y, Specia M, Huang S, Yuan C, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018;5:77–106.
4. National Cancer Registry Program of Egypt. Available: http://www.cancerregistry.gov.eg/. Accessed 10 Nov 2020.
5. Saleh B, Elhawary MA, Mohamed ME, El Zayat MS, Mohamed H. Gail model utilization in predicting breast cancer risk in Egyptian women: a cross-sectional study. Breast Cancer Research and Treatment; 2021. Available: https://doi.org/10.1007/s10549-021-06200-z
6. Dannenfelser R, Nome M, Tahiri A, Ursini-Siegel J, Vollan HKM, et al. Data-driven analysis of immune infiltrate in a large cohort of breast cancer and its association with disease progression, ER activity, and genomic complexity. Oncotarget. 2017;8:57121–57133. DOI: 10.18632/oncotarget.19078
7. Pruneri G, Vingiani A, Denkert C. Tumor infiltrating lymphocytes in early breast cancer. Breast. 2018;37:207–214. DOI: 10.1016/j.breast.2017.03.010
8. Hamouda SKM, *, Wahed ME, Abo Alez RH, Riad K. Robust breast cancer prediction system based on rough set...
theory at National Cancer Institute of Egypt. Computer Methods and Programs in Biomedicine. 2018;153:259–268.

9. Elsisi GH, Yousery Nada, Noha Rashad, João Carapinha, Ahmad O Noor, Diena M Almasri, Mostafa Al Zaidy, Ahmed Foad, Hussien Khaled. Cost-effectiveness of six months versus 1-year adjuvant trastuzumab in HER2 positive early breast cancer in Egypt. Journal of Medical Economics. 2020;23:6,575-580. DOI: 10.1080/13696998.2020.1724682

10. Hecht F, Carolina F. Pessoa CF, Luciana B. Gentile LB, Rosenthal D, Carvalho DP, Fortunato RS. The role of oxidative stress on breast cancer development and therapy. Tumor Biol. 2016;37:4281–4291. DOI: 10.1007/s13277-016-4873-9

11. Calaf GM, Urzua U, Termini L, Aguayo F. Oxidative stress in female cancers. Oncotarget. 2018;9(34):23824-23842.

12. Gurer-Orhana H, Incib E, Konyarc D, Sasod Land Suzenc S. The role of oxidative stress modulators in breast cancer. Current Medicinal Chemistry. 2018;25:4084-4101.

13. Griñan-Lison C, Blaya-Cánovas JL, López-Tejada A, Ávalos-Moreno M, et al. Antioxidants for the treatment of breast cancer: Are we there yet? Antioxidants. 2021;10:205. Available:https://doi.org/10.3390/antiox10020205

14. Devarajan A, Shih D, Reddy ST. Inflammation, infection, cancer and all that the role of paraoxonases, in oxidative stress and inflammation in non-communicable diseases - molecular mechanisms and perspectives in therapeutics. J. Camps, Ed., of Advances in Experimental Medicine and Biology. Springer, Cham. 2014: 824:33–41.

15. Moloney JN, Cotter TG. ROS signalling in the biology of cancer. Seminars in Cell & Developmental Biology. 2018;80:50–64.

16. Senghore T, Li YF, Sung FC, et al. Biomarkers of oxidative stress associated with the risk of potentially malignant oral disorders. Anticancer Research. 2018;38(9):5211–5216.

17. Athreya K, Xavier MF. Antioxidants in the treatment of cancer. Nutr. Cancer. 2017; 69:1099–1104.

18. Khan S, Ahmad S. Role of angiotensin converting enzyme (ACE) gene polymorphism in breast cancer among North Indian population. Annals of International Medical and Dental Research. 2019;5(6):17-23. DOI: 10.21276/aimdr.2019.5.6.PT3

19. Todd JH, Dowle C, Williams MR, Elston CW, Ellis IO, et al. Confirmation of a prognostic index in primary breast cancer. Br. J. Cancer. 1987;58:489-492.

20. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: Results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014:437971.

21. Gupta RK, Patel AK, Kumari R, Chugh S, Shrivastav C, Mehra S, Sharma AN. Interactions between oxidative stress, lipid profile and antioxidants in breast cancer: A case control study. Asian Pacific Journal of Cancer Prevention. 2012;13(12):6295-6298.

22. Derouiche S, Atoussi I, Guediri S. Assessment of hematological parameters, enzymes activities, and oxidative stress markers in saliva and blood of Algerian breast cancer patients receiving chemotherapy. J Biochem Tech. 2019;4:50-58. ISSN: 0974-2328

23. Savini I, Gasperi V, Catani MV. Oxidative stress and obesity; in: Obesity. Cham, Springer International Publishing. 2016; 65–86.

24. Kangari P, Farahany TZ3, Golchin A, Ebadorolahzadeh S, Salmaninejad A, Mahboob SA, Nourazarain A. Enzymatic antioxidant and lipid peroxidation evaluation in the newly diagnosed breast cancer patients in Iran. Asian Pac J Cancer Prev. 2018;19(12):3511-3515. DOI: 10.31557/APJCP.2018.19.12.3511

25. Sateesh R, Bitla AR, Budugu SR, Mutheeswariah Y, Narendra H, Phaneedra BV, et al. Oxidative stress in relation to obesity in breast cancer. Indian J Cancer. 2019;56:41-4.

26. Abdel-Salam OME, Youness ER, Hafez HF. The antioxidant status of the plasma in patients with breast cancer undergoing chemotherapy. Open J Mol Integr Physiol. 2011;1:29–35.
27. Sreenivasa Rao CS, Sarala Kumari D, Kumari DS. Changes in plasma lipid peroxidation and the antioxidant system in women with breast cancer. Int J Basic Appl Sci. 2012;1:429–38.

28. Czerska M, Mikolajewska K, Zieliński M, Gromadzińska J, Wąsowicz W. Today’s oxidative stress markers. Med Pr. 2015;66:393–405.

29. Nechuta S, Cai Q, Zheng Y, Milne GL, Cai H, Dai Q, et al. Urinary biomarkers of oxidative stress and breast cancer survival. Cancer Causes Control. 2014;25(6):701–7.

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