International Surgery Journal
Jina A et al. Int Surg J. 2020 Jan;7(1):210-216
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20195972

Original Research Article

Comparison of free radicals in blood in pre-operative and post-operative phases of breast malignancies: a clinicopathological study

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Received: 08 November 2019
Revised: 15 December 2019
Accepted: 16 December 2019

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ABSTRACT

Background: Various factors have been identified as influencing factors of breast cancer. The free radicals can cause increased oxidative stress by negatively affecting the body's nucleic acids, lipids and proteins leading to various illnesses including cancer. Therefore, this study was aimed at discovering the progress of treatment of breast carcinoma by exploring the connections of the disease with free radical injury.
Methods: The present study was conducted among 30 breast carcinoma patients received in the surgery department of BRD Medical College Gorakhpur. Determination of the levels superoxide dismutase (the procedure of photoluminescence), catalase (method of Cavarochi) and the lipid peroxidise was done. The results were presented as mean and standard error (SE). P value of <0.05 was considered as statistically significant.
Results: Among the total participants, 73% patients had infiltrating ductal carcinoma and 27% patients had intraductal carcinoma. The dismutase levels showed an increase in the post-operative patients for both the groups. The catalase levels and the lipid peroxide levels showed a reduction in the postoperative patients ($p<0.05$).
Conclusions: The present study result showed that the low amounts of SOD and catalase may not be sufficient to detoxify high amounts of free radicals. The administration of catalase could help in reducing the symptoms. Though, low amounts of SOD and catalase may not be sufficient to detoxify high amounts of free radicals. The administration of enzymes could help in the treatment of breast cancer patients.

Keywords: Free radicals, Oxidataion, Oxidative stress, Superoxide dismutase, Catalase, Lipid peroxidation, Infiltrating ductal carcinoma

INTRODUCTION

Breast malignancies account to the most common cancers among women with 25% of all cancers with an estimated incidence of 1.67 million cases in 2012.[1] The women from developed regions (794,000) have comparatively less number of cases than the women in less developed regions (883,000). Globally, breast cancer is the fifth leading cause of death, leading to an average of 522,000 cases yearly. It is the leading cause of death after lung cancer, which is 15.4% of all deaths with 198,000 deaths per year in the developed regions. In the developing regions it is the principal cause of deaths with 324,000 deaths annually, representing 14.3% of all the deaths. The number of cases varied from six to twenty per 100,000 together in East Asia and West Africa.[2]

Various factors have been identified as influencing factors of breast cancer, of which genetic, hormonal, and environmental factors play a major role. About 1/3rd of the factors depend on lifestyle modification (environmental factors) such as smoking, alcohol consumption, obesity (arising from lifestyle modification), and exposure to chest radiation.[3]

Free radicals have recently gained significance in health science due its various effects on living beings and its implication in numerous health conditions. The free radicals can cause increased oxidative stress by negatively affecting the body's nucleic acids, lipids and proteins[5]. The oxidative stress caused by the various actions of the free radicals can cause various disease conditions, such as diabetes mellitus, neurodegenerative disorders, cardiovascular conditions, respiratory diseases, optic illnesses, arthritis and certain cancers, such as colorectal, prostate, breast, lung, and bladder cancer.[4]

This study has been interesting to the author to study the effect of free radical in tumor promotion and oncogenesis. Free radicals are caused by the breakdown of cells during normal cellular metabolism. A free radical consists of one or more unpaired electrons, which makes it unsteady and reactive. The reactivity of the free radicals attract electrons from the normal cells to maintain their stability, thus making the normal cells unstable, and forming a new free radical.[4]

The free radicals include reactive oxygen and nitrogen and these are the principle elements in the initiation of cancer. These elements are responsible for the progression of tumor cells and enhancement of the metastatic potential of these cells. It is also perceived that these can provide contribution in the improvement of the condition in cancer patients undergoing radiotherapy.[5]

In comparison to other types of cancers, it has been observed that breast cancer has received more attention. There are various treatment strategies, such as adjuvant, neoadjuvant and palliative care based on each each characteristic molecular breast cancer subtype for evidence based preventative strategies, which has also failed to gain attention. This may be due to the under-representation of the studies associated with preventative strategies of breast malignancies or lack of long-term high quality preventive studies, which had not been possible to carry out to know the cause and effects of various strategies.[3] It has been observed from numerous reviews and research reports, that the data related to the association of environmental effects and their role as risk factors on the tumour characteristics are scant. Thus, this study was aimed at discovering the progress of treatment of breast carcinoma by exploring the connections of the disease with free radical injury

METHODS

The present study was conducted among the breast carcinoma patients received in the surgery department of BRD Medical College. The study was based on the data of the observations made during September 2017 to September 2018 in a tertiary teaching hospital. The study also included the patients who were treated in other hospitals but were referred for diagnosis or review, and were accessible for the present study during the period of data collection.

Study group

The study group included 30 patients with breast carcinoma, who were diagnosed on the basis of clinical history and examination and relevant radiological and hispathological examinations.

Statistical Analysis

The results were presented as mean and S.E along with sample sizes. Group comparisons were made using the Mann Whitney U-Test and analysis of Variance (ANOVA) with Tukey Post-hoc comparison. P value of <0.05 was considered as statistically significant. The statistical analysis was conducted using SPSS software.

Examination

A detailed history was taken along with the physical examination; findings of the mammography and USG abdomen of the samples were recorded as possible on a standardised proforma. For the data related to cytology, FNAC was done and aspirated after proper fixation was stained with hematoxylin and eosin, Geimsa etc.

Procedure

Specimen procedure: The surgical specimen (biopsy tissue) was obtained from the parts of a full grown tumor and preserved in 10% formalin saline. A standardised procedure was used to process the tissue and the paraffin lock in a histokinette. It was cut into a section of 2-3 micron on a rotator microtome and was stained with hematoxyline eosin, VG and reticulin.

Histopathological diagnosis: The histopathological diagnosis of the breast carcinomas were made according to the diagnostic criterion mentioned in the Acherman's text book of Surgical Pathology Vol. 1 and 2, Eighth Edition.

Blood samples

Preoperative blood samples were collected (5 ml blood) in plain vial, heparinised (5 ml) blood and similarly samples were collected postoperatively (after 3 weeks).

Enzyme analysis superoxide

The erythrocytes (0.5 ml) were washed three times with a 0.15 mol/l NaCl solution. The cells were centrifuged (400 X g) for 5 minutes and then suspended in 0.15 mol/l NaCl solution followed by sonication for 5 seconds at 4^0C. Drabkin reagent was used to measure the haemoglobin concentration in the hemosylate. Followed by this, haemoglobin was separated from the hemosylate by extraction in a chloroform-ethanol (3:5) mixture. The upper layer determined the superoxide dismutase activity (determination of enzyme).

Determination of enzyme

The superoxide dismutase activity was measured by photoluminescence method using Luminol.[6] The commercial kit for SOD using bovine Cu/Zn-SOD for the procedure, which is based on photochemical production of free radicals with photoluminescence, and was expressed in mg/kg Hb for erythrocytes.

Catalase

Method of Cavarochi was used to determine the catalase.[7] Hepanised venous blood was washed three times with 0.15 mol/l NaCI solution. After centrifugation (400 x g; 5 min), the erythrocytes were hemolyzed by adding triple volume of distilled water. The Hb concentration in the hemosylate was measured using Drabkin's solution.

Methods

Step I: 1 ml of reaction mixture containing chloride -1 mmol/l H202 in phosphate buffer (0.1 mole/l; pH 7.8) along with the hemolysate.

Step II: The mixture was incubated for 10 minutes.

Step III: The reaction was stopped by adding a solution containing 1.476 mmol/l - 4-aminoantipyrene in phosphate buffer (0.1 mol; pH 7.0; 1250 u/l peroxidase and 0.05% phenol.

Step IV: Pye uni chem spectrophometer was used to measure the absorbance of the reaction product, which was 10.5 nm. The procedure was expressed in Kat/mg.

Lipid peroxidase

Serum lipid peroxidase was determined among pre and post operative patients with breast carcinoma.

Principle

The method included adding of 2.5 ml of 20% TCA and 1.0 ml of 0.67% TBA to 0.5 ml of serum. The mixture was heated in a boiling water bath for 30 minutes. Chroinogen was extracted using n-butyl alcohol and the absorbation of the organic phase was determined at the wave length 530 nm. Malonaldehyde (nmol/ml) was used as reference standard.

Reagents

Trichloroacetic acid (TCA) in distilled water. 0.05 M of sulphuric acid, Sodium sulphate solution (2 M): 90 ml of distilled water and 284 gm of anhydrous sodium sulphate was taken and dissolved by heating and stirring. The volume was made upto 100 ml to prepare a *2* M solution. TBA (reagent) was dissolved in 2 M sodium sulphate by heating.

n-butyl alcohol (extraction)

Standard solution: malonaldehyde-1 bis-diethyl-acetal) 1,1,3,3' tetramethoxypropane was dissolved in 0.15 M, sulphuric acid to prepare a 10 uM solution.

Standard procedure

0.5 ml serum was added to 2.5 ml of TCA and left for 10 min at room temperature. It was centrifuged at 3500 rev/min for 10 min. Decant supernatant. The precipitate was washed with 0.05 M sulphuric acid. 2.5 ml of sulphuric acid (0.05 M) and 3.0 ml of 0.2 mg/dl TBA in 2 M sodium sulphate was added to the precipitate. It was kept in boiling water for 30 minutes for coupling LPO. Further, it was cooled in running tap water. Chromogen (coloured Product of Pink Colour) was extracted with 4.0 ml n-butyl alcohol by vigorous shaking. Separation of organic phase was facilitated by centrifugation at 3000 rev/min for 10 min. Reading was taken at wave length of 530 nm. The standard curve was linear upto - 21.2 mmol/ml malonaldehyde. Serum values were calculated with standard curve.

RESULTS

Age distribution

A total of 30 patients were included in the study, of which 50% of the women belonged to the age group of 40 to 49 years. This was followed by the age group of 50-59 years (40%), while 6.6% and 3.3% belonged to 30-39 years and 60-70 years respectively.

Table 1: Age distribution of patients with CA breast.

Age group (year)	No. of patients	%
30-39	2	6.6
40-49	15	50
50-59	12	40
60-70	1	3.3
Total	30	100

CA- cancer.

Type of carcinoma

Among the 30 participants, 22 (73%) patients had infiltrating ductal carcinoma and 8 (27%) patients had intraductal carcinoma.

Dismutase levels

The mean value of the superoxide dismutase levels (SOD) for the pre and post-operative patients (22 patients) with infiltrating ductal carcinoma was 0.90 and 0.72 respectively. The SE value for the same group of the patients was 0.07 and 0.04 for the pre and post-operative group respectively. The mean and SE value of the superoxide dismutase levels for the pre and post-operative patients (8 patients) with intraductal carcinoma

was 0.82 and 0.62 (mean value) and 0.06 and 0.03 (SE value) respectively.

Table 2: Superoxide dismutase levels.

Diagnosis	Superoxide dismutase (mg/gm Hb)	
	Preoperative	Postoperative
L infiltrating ductal carcinoma		
Mean	0.90	0.72
SE	0.07	0.04
H. intraductal carcinoma		
Mean	0.82	0.62
SE	0.06	0.03

SE- Standard error

Catalase levels

The mean and SE value of the catalase levels for the pre and post-operative patients (22 patients) with infiltrating ductal carcinoma was 140.8 and 130 (mean value) and 7.7 and 7.5 respectively. The mean and SE value of the catalase levels for the pre and post-operative patients (8 patients) with intraductal carcinoma was 127 and 123 (mean value); 7.5 and 6.0 (SE value) respectively.

Table 3: Catalase levels.

Diagnosis	Catalase (pKat/gm Hbj	
	Preoperative	Postoperative
Infiltrating ductal carcinoma		
Mean	140.8	130.0
SE	7.7	7.5
Intraductal carcinoma		
Mean	127	123.0
SE	7.5	6.0

Lipid peroxide levels

The mean and SE value of the lipid peroxidise levels for the pre and post-operative patients (22 patients) with infiltrating ductal carcinoma was 5 and 3.40 (mean value); 1.02 and 0.75 respectively. The mean and SE value of the lipid peroxidase levels for the pre and post-operative patients (8 patients) with intraductal carcinoma was 6 and 4.20 (mean value); 1.05 and 0.85 (SE value) respectively.

Table 4: Lipid peroxidase levels.

Diagnosis	Lipid peroxide (nmol/ml)	
	Preoperative	Postoperative
Infiltrating ductal carcinoma		
Mean	5.00	3.40
SE	1.02	0.75
Intraductal carcinoma		
Mean	6.00	4.20
SE	1.05	0.85

Table 5: Serum lipid peroxidase of pre and post operative patients.

No. of patients	Pre-operative (mean±SE; nmol/mI)	Post-operative (mean±SE; nmol/ml)
22	5.0±1.02	3.4±0.75

Table 6: Serum lipid peroxidase in intraductal carcinoma.

No. of patients	Pre-operative (mean±SE; nmol/ml)	Post-operative (mean±SE; nmol/ml)
8	6.0±1.05	4.2±0.85

Table 7: Activity of antioxidant enzymes in erythrocytes in intraductal carcinoma (superoxide dismutase and catalase).

No. of patients	Parameters	Pre-operative (mean±SE)	Post-operative (mean±SE)
8	SOD (mg/gm Hb)	0.82±0.06[a]	0.62±0.03[a]
	Catalase (uKat/gm Hb)	128.7±7.5[a]	123±6.0[a]

a=Significant (p<0.05)

Table 8: Activity of antioxidant enzymes in erythrocytes in infiltrating ductal carcinoma (superoxide dismutase and catalase).

No. of patients	Parameters	Pre-operative (mean±SE)	Post-operative (mean±SE)
22	SOD (mg/gm Hb)	0.90±0.07[a]	0.72±0.04[a]
	Catalase (uKat/gm Hb)	140.8±7.7[a]	130±7.5[a]

a = Significant (p<0.05);SOD- Superoxide dismutase.

Antioxidant enzymes in intraductal carcinoma

The activity of antioxidant enzymes in erythrocytes in intraductal carcinoma shows that among the eight pre and post-operative patients, the mean and SE of superoxide dismutase was 0.82±0.06 and 0.62±0.03 respectively, while for catalase it was 128.7±7.5 and 123±6.0 respectively. All the values were significant (p<0.05).

Antioxidant enzymes in infiltrating ductal carcinoma

The activity of antioxidant enzymes in erythrocytes in infiltrating ductal carcinoma shows that among the 22 pre and post-operative patients, the mean and SE of superoxide dismutase was 0.90±0.07 and 0.72±0.04 respectively, while for catalase it was 140.8±7.7 and 130±7.5, respectively All the values were significant (p<0.05).

Control values of anti-oxidants

The control values of the anto-oxidants superoxide dismutase, lipid peroxidase and catalase were 0.48 mg/gm Hb, 2.10 nmol/ml and 112.40 pKat/gm Hb.

Table 9: Control values of anti-oxidants.

S. no.	Name	Control value	Units
1	Superoxide dismutase	0.48	Mg/gm Hb
2	Lipid peroxidase	2.10	nmol/ml
3	Catalase	112.40	pKat/gm Hb

DISCUSSION

Breast cancer is a leading cause of death among women in the developed and developing countries. Many efforts have been made to increase awareness about breast health and improve access to health care services, and breast cancer screening programs.[8] The formation and activity of free radicals are known to cause various types of diseases including cancers. The free radicals bind to the normal cells, thereby producing new free radicals. It is necessarily required to reduce the damage caused to the normal cells by these free radicals.[5]

A total of 30 patients were included in the study, of which 50% of the women belonged to the age group of 40 to 49 years. The findings can be supported by the study conducted by El-Hefny, Karomova and Afandiev, which revealed that the mean age of the preoperative group of patients was 48.6±7.2 years and the post-operative group was 49.6±8.3 years.[11]

The present study shows that among the 30 participants, 22 (73%) patients had infiltrating ductal carcinoma. According to the Breast Cancer Organization, about 80% of all breast cancers are invasive or infiltrating ductal carcinomas, which is similar to the findings of the present study. About 180,000 women in the United States are diagnosed as invasive breast cancer and most of them are detected with invasive ductal carcinoma. The Breast Cancer Organization further states that though the possibility of occurrence of the disease is at any age, it mostly occurs in older women above 55 years. The present study shows that only five patients with infiltrating ductal carcinoma were above 55 years and the remaining were in between 35 and 55 years of age.[9]

The present study shows that 8 (27%) out of 30 patients had intraductal carcinoma. According to Vaidya et al intraductal carcinoma accounts for 20 to 25% of the newly detected neoplasms and 17 to 34% of the cancers detected through mammography.[10] It is estimated that about 14 to 53% of the intraductal carcinoma cases progress to infiltrating ductal carcinoma.[10] In a study conducted by Narod, Iqbal, Giannakeas and Sun, it was observed that the statistics given by surveillance, epidemiology and end results (SEER) found that the diagnosis of ductal cancer was made at an average age of 53.8 years and the death rate was 3.3% over a 20 year period after the detection of the disease. Nevertheless, the death rate increased to 7.8% among the women who were diagnosed with ductal carcinoma before 35 years.[12] The present study also showed that the average age of the patients with intraductal carcinoma was 48.5 years, which is probably the average age of diagnosis of such carcinomas.

Evidences incriminate the presence of the oxygen derived free radicals in the pathogenesis of breast cancer. These free radicals cause injury to the cell membrane of the normal cells, mitochondria and macromolecules, proteins, lipids, and DNA. These free radicals involve in the cellular proliferation. Elevated levels of SOD has been observed among patients with breast carcinoma, though few studies show reduced SOD levels.[11] The study conducted by Mahajan et al shows that normal women had significantly higher (10.0-15.5, mean-13.1±2.3) SOD levels than the preoperative (4.4-14.5, mean- 9.4±2.6) and the postoperative (8.8-20, mean-11.8±2.5) women with different stages of breast carcinoma.[13]

The present study shows that the mean SOD levels for preoperative patients was 0.90 and post-operative patients was 0.72 among the women with infiltrating ductal carcinoma. In the patients with intraductal carcinoma, the mean value of SOD levels among preoperative and postoperative patients was 0.82 and 0.62 respectively. It showed that the SOD level was higher in preoperative women, which reduced after the treatment. The findings were contrary to the study conducted by Mahajan et al which shows that the mean SOD values were higher in the postoperative (11.8±2.5) women than the preoperative (9.4±2.6) women with breast carcinoma.[13] This indicated an improvement in SOD activity in postoperative patients than in preoperative patients.[11] In the study conducted by Neghaldar et al, it was observed that the SOD activity decreased in the patients with breast cancer. This indicated high production of free radicals in their body.[12]

Catalase causes breakdown of hydrogen peroxide (H_2O_2) to water and oxygen. The present study shows that the mean value of the catalase levels measured at pKat/gm Hbj showed a higher value for preoperative (140.8 at pKat/gm Hbj) than postoperative (130.0 at pKat/gm Hbj) patients with infiltrating ductal carcinoma. The preoperative patients showed a increased level of 10.8 pKat/gm Hbj. Among the patients with intraductal carcinoma, the mean value in preoperative patients was 127 at pKat/gm Hbj while in postoperative patients it was 123 at pKat/gm Hbj. In the study conducted by Singh et al, the catalase values decreased among the patients who had undergone cyclophosphamide, doxorubicin, and 5-fluorouracil in comparison to the control group.[14] The catalase levels showed reduced values at every (12 weeks: 3348.04±842.79 U/g Hb, 18 weeks:

3360.85±835.54 U/g Hb and 26 weeks: 3350.36±835.87 U/g Hb) determined interval of the treatment process. In the study conducted by Negahdar et al, it was observed that the catalase activity decreased in the patients with breast cancer.[15] SOD and catalase are the essential antioxidant enzymes, which can cause the elimination of reactive oxygen metabolites (ROMs) and glutathione peroxidise. These antioxidant enzymes also act as anti-carcinogens and also prevent the transformation of the normal cells into free radicals. SOD has the capability to block the mutation caused by potassium superoxide in mammalian cells and catalase can inhibit the function of the environmental mutagens. Catalase can prevent the occurrence of chromosomal aberration caused by xanthine oxidase in Chinese hamsters and also put a stop to the onset of neoplastic transformation of normal cells in fibroblast and epidermal keratinocytes.[15] Thus, the reduction of SOD and catalase enzymes indicate higher production of free radicals, though the levels of the enzymes must be increased with subsequent rounds of treatment.[15]

The findings of the present study are also supported by the study conducted by El-Bindary et al, which also shows that the SOD and catalase levels were reduced in pre treated breast cancer patients. It was due to the high production of free radicals leading to the accumulation of ROMs.[16] In the study conducted by El-Hefny et al, it was observed that The levels of catalase activity decreased significantly in all the stages of breast cancer patients in comparison to the control group ($p<0.05$). The catalase activity was 32.73% in the preoperative group, 29.30% in the postoperative group and 30.53 in the control group.[9] According to the study conducted by Malik et, al. the preoperative and postoperative values of SOD (1.38±0.16 µg/dl vs. 0.92±0.81 µg/dl), catalase (4.33±0.74 µg/dl vs. 1.69±1.18 µg /dl) and glutamine peroxidise (GPx) (0.79±0.34 µmol/ml vs. 0.18±0.05 µmol/ml) showed a highly significant pattern respectively among the patients with breast cancer. It indicated the reduction of the values after postoperative management.[17]

Malonialdehyde (MDA) is a marker of lipid peroxidation. Free radicals initiate the lipid peroxidation process. MDA is a final product of lipid peroxidation and an increase in the levels of MDA indicates an increased production of free radicals.[18] In the study conducted by Gonenc et al., the serum and tissue MDA was decreased in breast cancer patients compared to the benign breast disease ($p<0.05$). The tissue total antioxidant capacity was higher in the patients with breast cancer than the patients with benign breast disease ($p<0.05$). Total cholesterol and HDL cholesterol was high in benign breast disease ($p<0.05$) than breast cancer patients. It showed that the lipid peroxidation was higher in patients with benign breast disease than in breast cancer patients.[18] The present study showed similar findings with increased lipid peroxidase levels in both, preoperative (mean value-6.00) and postoperative (mean value-4.20) patients in intraductal carcinoma than infiltrating ductal carcinoma (preoperative patients mean value-5.00 and postoperative patients mean value- 3.40). The lipid peroxidase levels were lower in postoperative patients than preoperative patients for both the types of cancers.

In the study conducted by Ray et al, it was observed that, the concentration of MDA was significantly higher in stage II ($p<0.001$), stage III ($p<0.01$), postmenopausal ($p<0.005$), and premenopausal ($p<0.02$) women with breast cancer than the control group. The catalase activity was reduced in all the study groups. This was probably because of elevated ROM production, as elevated ROM caused decreased catalase activity, which is an indicator of oxidative stress and carcinogenesis. Additionally, it was also estimated that high SOD and GPx values were probably due to a high amount of ROM production in the blood.[20] Thus, the levels of SOD and GPx were insufficient to detoxify the high amounts of H2O2 and H2O which led to the development of OH radical and MDA, where both the products were highly dangerous and initiated and promoted carcinogenesis.[21] In the study conducted by Zarrini et al, the patients had higher lipid peroxidation at advanced stage of breast cancer, which indicated high oxidative stress and the production of highly dangerous substances such as MDA.[22] Therefore, the administration of catalase could help in the reduction of such products and help in the management of breast cancer patients.[20]

CONCLUSION

This present study indicates that the administration of catalase could help in reducing the symptoms of the breast cancer primarily. Though, low amounts of SOD and catalase may not be sufficient to detoxify high amounts of free radicals. The administration of enzymes could help in the treatment of breast cancer patients. However, further clinical research is required to be done prior to drawing a conclusion.

ACKNOWLEDGEMENTS

We are thankful to our students in collecting data and helping us tabulate them and also thank our clerical staff in helping us with the typing part of this paper.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Jina A, Singh UC. Comparison of free radicals in blood in pre-operative and post-operative phases of breast malignancies: a clinicopathological study. Int Surg J 2020;7:210-6.