

Original Article

A COMPARATIVE STUDY OF SERUM IRON AND FERRITIN BETWEEN PRE-TREATED BREAST CANCER PATIENTS WITH HEALTHY CONTROLS OF THE SAME AGE GROUP

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ABSTRACT:

Introduction: Breast cancer is one of the leading cause of cancer related deaths in women and there are differences in breast cancer recurrence, aggressiveness and incidence between premenopausal and postmenopausal women. **Materials & Methods:** The study was conducted in the Department of Biochemistry in collaboration with Department of Surgery and Radiotherapy, G.G.S. Medical College Faridkot. Serum Iron & Ferritin levels were compared in the premenopausal and postmenopausal breast cancer women with the age and sex matched healthy controls of the same age group. All the patients included were pretreated and had not undergone any Surgery, Chemotherapy, Radiotherapy and Hormone therapy. **Results:** Iron and ferritin levels were found to be lower in premenopausal women than controls ($p < 0.05$ and $p < 0.05$). But in postmenopausal women iron and ferritin levels were found to be higher in postmenopausal women as compared to controls ($p = 0.14$ and $p < 0.05$). **Conclusions:** Iron is a double edge sword as both low and high levels of iron can cause the increased risk of breast cancer.

Key words: Breast Cancer, Iron, Ferritin, Premenopausal, Postmenopausal.

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This article may be cited as: Panag KS, Sidhu DS, Goyal G, Banipal RS, Singh J. A comparative study of serum iron and ferritin between pre-treated breast cancer patients with healthy controls of the same age group. J Adv Med Dent Scie Res 2017;5(11):13-19.

Access this article online	
<p>Quick Response Code</p> 	Website: www.jamdsr.com
	DOI: 10.21276/jamdsr.2017.5.11.04

INTRODUCTION:

Cancer is not a new disease. The word cancer is derived from French word “chancre” originally meaning “crab”. Written descriptions of it can be found on Egyptian papyrus dating back to roughly 1600 BC. The Greek physician Hippocrates is believed to be the first person to use the word “carcinosis”, which describes the crab like way that both the ulcer forming and non-ulcer forming tumors spread. Overtime the word shortened to “cancer”. The oldest description of cancer was discovered in Egypt and dates back to approximately 1600 BC.⁽¹⁾ Alternatively, patients often saw it as divine punishment. In the 18th century, a wide variety of medical explanations were proposed, including a lack of sexual activity, too much sexual activity, physical injuries to the

breast, curdled breast milk, and various forms of lymphatic blockages, either internal or due to restrictive clothing.⁽²⁾

Cancer constitutes an enormous burden on society in more and less economically developed countries alike. The occurrence of is increasing because of the growth and ageing of the population, as well as increasing prevalence of established risk factors such as smoking, overweight, physical inactivity and changing reproductive patterns associated with urbanization and economic development. Based on GLOBOCAN estimates, about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide.⁽³⁾

Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2012 (second most common cancer overall). This represent about 12% of new cancer cases and 25% of all cancers in

women.⁽⁴⁾Times of India (Madan Mohan 2013) Punjab's cancer cases exceed ...There are 90 cancer patients for every 1lakh population in Punjab, which is more than national average of 80 per lakh. The Malwa region of the state has highest average of 136 cancer patients per 1 lakh.⁽⁵⁾ Times of India (Sengupta 2011) A train ride to cancer care...Cancer affected southern districts of Punjab ,Bathinda, Faridkot, Moga, Muktsar, Ferozpur, Sangrur and Mansa known together as the Malwa region which is also Punjab's cotton belt. Here the farmers and families are grappling with cancer and health problems that have crept into their homes through the backdoor as the farmers of India's grain bowl fed the nation.⁽⁶⁾

Breast cancer starts in the cells of the breast. The breast tissue covers an area larger the just the breast. It extends up to the collar bone and from the armpit across to the breast bone in the center of chest. The breasts sit on the chest muscles that cover the ribs. Each breast is made of glands, ducts (thin tubes) and fatty tissue. Lobules are group of glands that can produce milk. Milk flows from the lobules through a network of ducts to the nipple. The nipple is in the center of darker area of skin called the areola. Fatty tissue fill the spaces between the lobules and ducts and protects them.⁽⁷⁾Breast cancer is known to be influenced by many factors which includes-family history, race, ethnicity, gender, age, dense breast tissue, obesity, oxidative stress, genetic factors, oestrogen excess and environmental and dietary factors.⁽⁸⁾The size, stage, rate of growth, and other characteristics of a breast cancer determine the kinds of treatment. Treatment may include surgery, drugs (hormonal therapy and chemotherapy), radiation and immunotherapy⁽⁹⁾.Risk factors for developing breast cancer include female sex,obesity, lack of physical exercise, drinking alcohol, hormone

replacementtherapy during menopause, ionizing radiation, early age at first menstruation, having children late or not at all, older age, family history and BRCA 1and BRCA 2 genetic factors. About 5–10% BRCA 1and BRCA 2 genetic factors thought to contribute to pooroutcome due to genes inherited from a person's parents.⁽¹⁰⁾

But there are several other risk factors that exist like family history, race and ethnicity, gender, ageing, genetic factors, dense breast tissue and oxidative stress. Simply being a woman is not the main risk factor for developing breast cancer. Men also develop breast cancer, but this disease is about 100 times more common among women than men.⁽¹¹⁾

Iron is an essential growth nutrient and has equal importance to oestrogen in female metabolism and (development and changes in its concentration during menopausal transition, might have key role in the development and recurrence of breast cancer in women, because of blood loss premenopausal women have higher dietary requirement for iron to prevent iron deficiency than men or postmenopausal women. In general iron concentrations are much lower in premenopausal women than in post-menopausal women.⁽¹²⁾

Ferritin is an iron storage protein with a capacity of binding up to 4500 atoms of iron and transferrin an iron dependent protein with two binding sites for iron are much less saturated in premenopausal women than in postmenopausal women.⁽¹²⁾Iron is an essential micronutrient for normal cellular physiology but low iron levels can also result in cancer as angiogenesis is necessary for any tumor to grow beyond a certain volume and has an important role in tumor progression, malignancy and recurrence. This process is regulated by several pro-angiogenic factors like VEGF (Vascular Endothelial Growth Factor) and Basic Fibroblast growth factor and anti-angiogenic (e.g. thromspodin 1) produced by both tumor cells and stroma⁽¹³⁾.

Cells buried in the center of tumor mass receive inadequate oxygen and nutrient supply and this deprivation results in hypoxic cascade in which hypoxia inducible factor 1 alpha stabilizes and up-regulate gene stimulating angiogenesis, resulting in formation of new vasculature, which penetrates into the tumor core. Increased VEGF concentration has been reported in patients with cancer.⁽¹⁴⁾

Though iron is an essential micronutrient but an excess can result in cell injury. Iron in low molecular weight forms may play a catalytic role in the initiation of free radical reactions. The resulting oxy radicals have the potential to damage cellular lipids, nucleic acids, proteins and carbohydrates leading to impairment of cellular function and integrity. The rate of free radical production must overwhelm the cyto-protective defense of cells before injury occurs.⁽¹⁵⁾Iron may induce Oxidative stress (OS) via production of reactive oxygen species (ROS) facilitating mammary carcinogenesis. The role of iron in relation to OS is a potential risk factor in the development of breast cancer.⁽¹⁶⁾Besides this excess iron is also an etiological factor for development of breast cancer as iron is well known for catalyzing Fenton/Haber-Weiss or auto oxidation reactions, that can lead to the formation of reactive oxygen species(ROS) and lipid peroxidation, as well as their products which give rise to mutagenic aldehydes, such as 4-hydroxy nonenal. In conjunction with high local concentrations of oestrogen in the breast from either endogenous (e.g. increased COX-2) or exogenous (e.g. HRT use or intake of high fat diet) sources, iron can catalyze the redox cycling of catechol oestrogen metabolites quinone and semiquinone, which generate ROS which act as secondary messengers in intracellular signaling cascades which can maintain and induce oncogenic phenotype of cancer cells.^(17,18)Ferritin is a sensitive indicator of iron deficiency, thus the main clinical application of serum ferritin measurement is in differential diagnosis of anemia. Ferritin concentration may increase in case of overload (hemochromatosis or hemosiderosis), infection or inflammation, neurodegenerative disorders, malignancy and destruction of liver tissue⁽¹⁹⁾

Iron is necessary for cell proliferation and iron metabolism is influenced by estrogen hormones interactions between iron and oestrogen may synergistically promote breast

cancer. In condition with elevated iron increased ferritin concentrations may have a protective role preventing oxidative stress caused by excess iron.⁽²⁰⁾

Ferritin is a prime source of free iron and elevated ferritin levels are observed in many breast cancer patients. Ferritin may be the principle source of free iron that might enhance process of tumorigenesis.⁽²¹⁾

MATERIALS AND METHODS

The present study was conducted in the Department of Biochemistry in collaboration with the Department of Surgery and Radiotherapy, G.G.S. Medical College, Faridkot, Punjab. The study included 100 newly diagnosed breast cancer patients and 100 age matched controls. The patients were further sub-grouped into 50 premenopausal and 50 postmenopausal women. Similarly controls were further sub-grouped into 50 premenopausal and 50 postmenopausal women. Informed consent was taken from all the participants who were included in this study and those who were willing to participate and satisfying the inclusion criteria were included. The breast cancer patients who were selected for the study had not undergone any form of treatment like Surgery, Chemotherapy, Radiotherapy and Hormone therapy. All of them were freshly diagnosed after the confirmation of breast cancer by FNAC. Blood samples were withdrawn before starting any form of further treatment. The controls were not having any history of disease like diabetes mellitus, liver or renal disease, anemia of any kind or any other disease that can affect the

concerned parameters. Blood samples were run for serum Iron and Ferritin

1. Serum Iron (in µg/dl) (PRINCIPLE): Under acidic conditions, Fe⁽³⁺⁾(ferric iron) bound to the protein transferrin is released. In the presence of the reducing agent ascorbic acid, Fe³⁺ is reduced to Fe²⁺(ferrous iron) which forms a blue complex with Ferene The absorbance of the complex is measured using a bichromatic (600,700 nm) end point technique which is directly proportional to the concentration of iron in the serum⁽²²⁾

It was run on Fully Automated Siemens Dimension Xpand plus auto analyser.

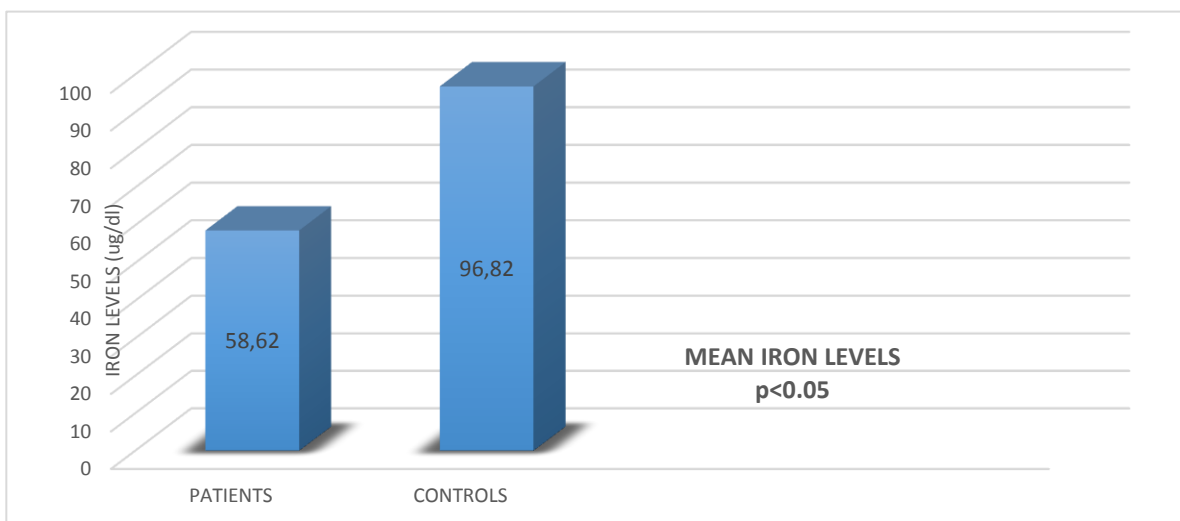
2. Serum Ferritin (in ng/ml) (PRINCIPLE): Ferritin is a solid phase, enzyme labeled chemiluminescent immunometric assay. The solid phase is coated with monoclonal murine m anti-ferritin antibody. The liquid phase consists of alkaline phosphates (bovine calf intestine) conjugated to polyclonal goat anti-ferritin antibody. The patient and the reagent are incubated together with the coated bead for 30 minutes. During this time ferritin in the sample forms antibody sandwich complex with monoclonal murine anti-ferritin antibody on the bead and the enzyme conjugated polyclonal anti- ferritin antibody in the reagent. Unbound patient sample and enzyme conjugate are then removed by centrifugal washes. Finally, chemiluminescent substrate is added to the test unit containing the bead and the signal is generated in proportion to the bound enzyme.

It was run on Fully Automated Chemiluminescence Siemens Immulite 1000.

RESULTS IRON: (PREMENOPAUSAL PATIENTS & CONTROLS)

1. SERUM IRON

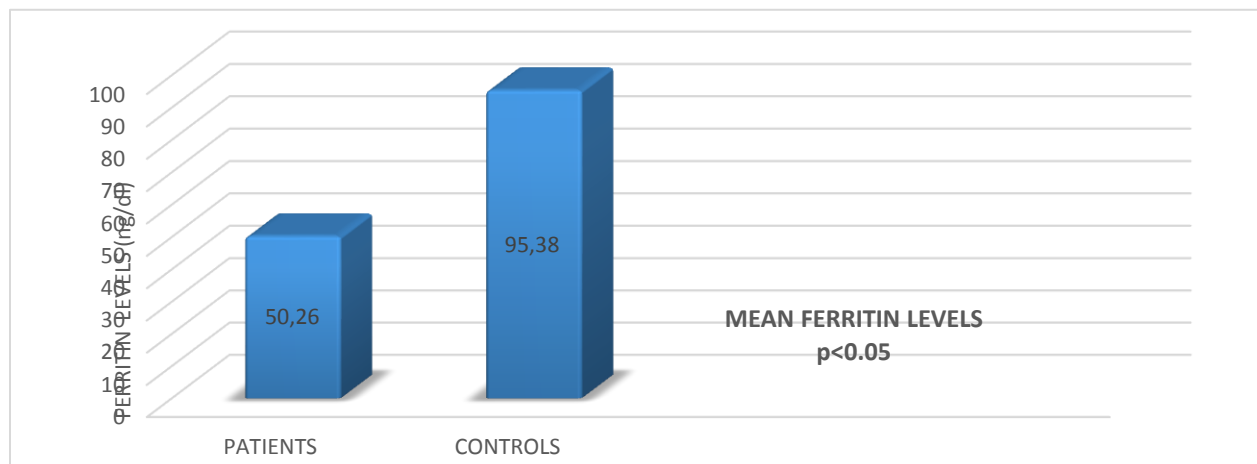
IRON VALUES	PATIENTS	CONTROLS	p value
MEAN	58.62	96.82	p<0.05 Significant
SD	25.71	7.31	
Mean Rank	27.65	73.35	Man Whitney U= 2,392.50



The iron levels were compared between premenopausal patients & premenopausal controls. In this study the iron levels were found to be significantly lower in breast cancer patients as compared to controls with Mean \pm SD= 58.62 \pm 25.71 and Mean rank =27.65 as compared to controls with Mean \pm SD 96.82 \pm 7.31 and Mean rank=73.35 and p value was found to be highly significant(p<0.05) with Man Whitney U =2,392.50.

IRON LEVELS	PATIENT	CONTROL	P value
MEAN	94.2	86.8	p=0.143
SD	25.20	6.67	Non-Significant
Mean Rank	54.75	46.25	Man Whitney U=1037.50

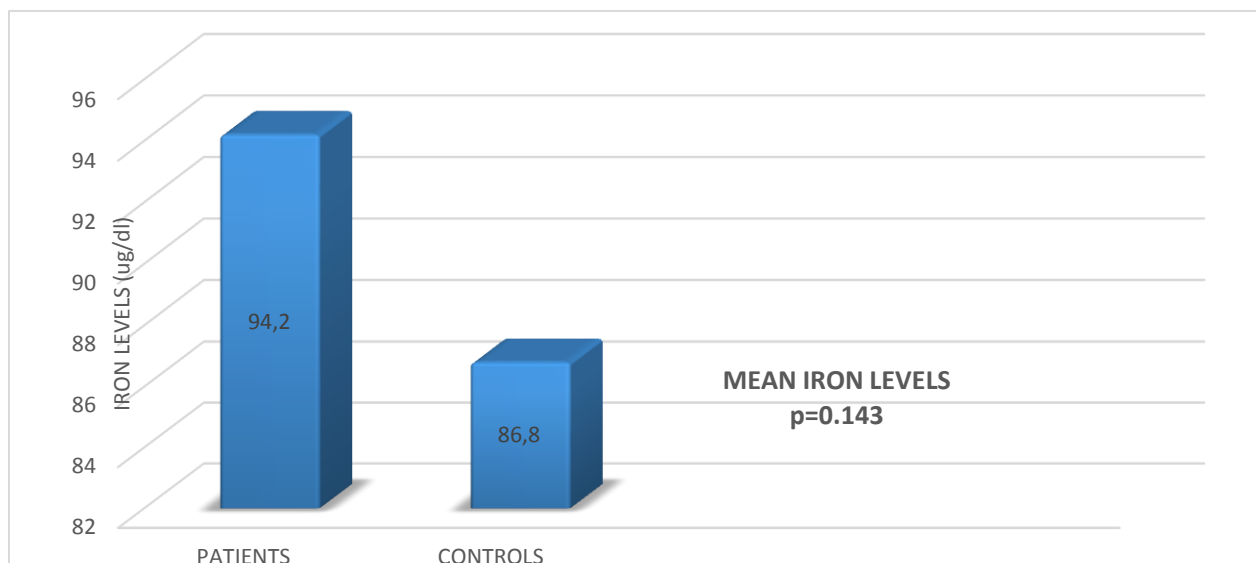
2. SERUM FERRITIN



The Ferritin levels were compared between premenopausal patients & premenopausal controls. In this study the Ferritin levels were found to be significantly lower in breast cancer patients as compared to controls with Mean \pm SD = 50.26 \pm 48.16 and Mean Rank=32.77 as compared to controls with Mean \pm SD=95.38 \pm 9.92 and Mean Rank =68.23 with Mann Whitney U=2136.50 and p value was found to be significant. (p<0.05).

POSTMENOPAUSAL PATIENTS & CONTROL

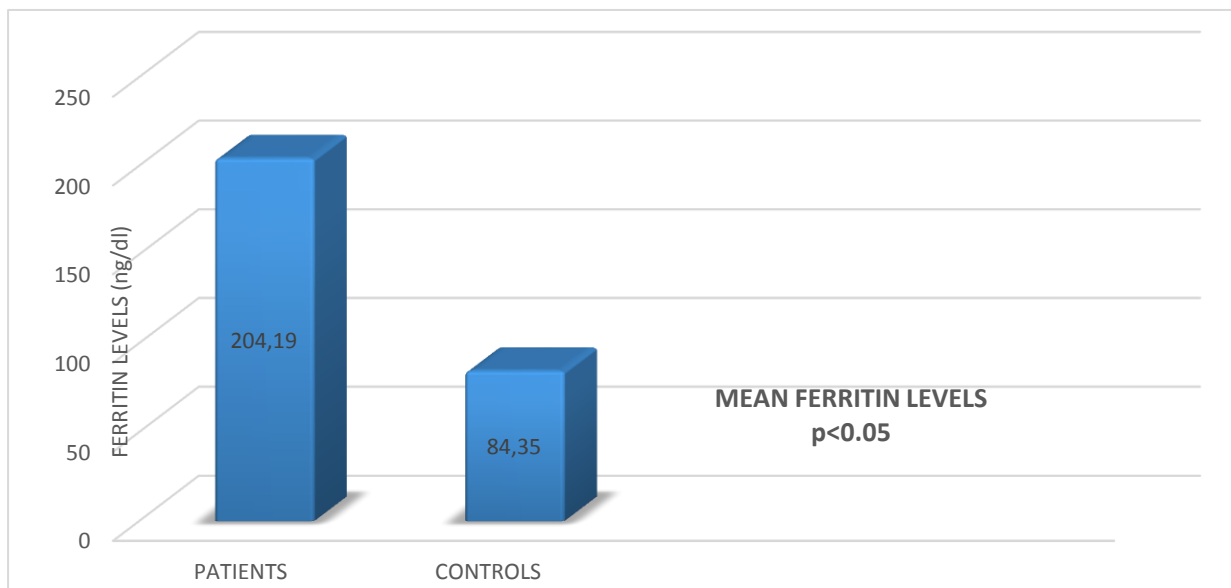
1. SERUM IRON



FERRITIN VALUES	PATIENTS	CONTROLS	P value
MEAN	50.26	95.38	p<0.05
SD	48.16	9.92	Significant
Mean rank	32.77	68.23	Man Whitney U=2136.50

The iron levels were compared between postmenopausal patients & postmenopausal controls. In this study the iron levels were found to be higher in breast cancer patients as compared to controls with Mean± SD = 94.2±25.20 and Mean Rank 54.75 as compared to controls with Mean ± SD 86.8 ± 6.67 and Mean Rank=46.25 with Man Whitney U=1037.50 and p value was found to be non-significant (p=0.143).

2. SERUM FERRITIN:



FERRITIN VALUES	PATIENTS	CONTROLS	p value
MEAN	204.19	84.35	p<0.05
SD	117.24	25.80	Significant
Mean Rank	67.25	33.75	Man Whitney U=412.50

The Ferritin levels were compared between postmenopausal patients & postmenopausal controls. In this study the Ferritin levels were found to be significantly higher in breast cancer patients as compared to controls with Mean ± SD=204.19 ± 117.24 and Mean Rank 67.25 as compared to controls with Mean ± SD=84.35 ± 25.80 and Mean Rank 33.75 with Man Whitney U=412.50 and p value was found to be significant(p<0.05).

DISCUSSION:

The distribution iron levels was found to be significantly lower in premenopausal patients as compared to controls with Mean±SD=58.62±25.62 and Mean rank=27.65 as compared to controls with Mean±SD=96.82±7.31 and Mean rank=73.35 and Man Whitney U=2392.50 and p value<0.05.

Low iron levels are also reported by the study of BasimaSadiq, 2015 in which patients with breast cancer had Mean±SD=28.5±9.48 as compared to controls with Mean±SD=91.84±23.25 and p value was found to be statistically significant⁽²³⁾(p<0.01).

Deficiency of iron along with high oestradiol in premenopausal women can lead to increased VEGF formation, angiogenesis, metastasis and consequently high recurrence and iron deficiency could be additional important factor in enhancing VEGF concentrations in premenopausal women. Iron deficiency leads to increase in HIF-1 α stabilization and angiogenesis by two different mechanisms: by lowering concentration of HIF-degrading prolyl-4-hydroxylase because iron

is a cofactor of this enzyme and by decreasing oxygen tension (increased hypoxia) in the body as result of the presence of fewer blood cells because of menstruation. HIF-1 α prolyl-4 hydroxylase is an enzyme that hydroxylates HIF 1 α and is iron protein, which leads to increased VEGF concentrations and angiogenesis⁽¹²⁾

The distribution of ferritin levels was found to be significantly lower premenopausal patients as compared to controls with Mean \pm SD=50.26 \pm 48.16 and Mean Rank=32.77 and as compared to controls with Mean \pm SD=95.38 \pm 9.92 and mean rank=68.23 and Man Whitney U=2136.50 and p value<0.05.

Since the iron concentrations was found to be lower in premenopausal breast cancer patients and ferritin is an iron storage protein so the concentration of ferritin was also found to be lower in breast cancer patients due to the decreased iron concentrations.

The distribution iron levels was found to be higher in postmenopausal patients as compared to controls with Mean \pm SD=94.2 \pm 25.20 and Mean rank=54.75 as compared to controls with Mean \pm SD=86.8 \pm 6.67 and Mean rank=46.25 and Man Whitney U=1037.50 and p value=0.143.

Though iron is an essential micronutrient but an excess can result in cell injury. Iron in low molecular weight forms may play a catalytic role in the initiation of free radical reactions. The resulting oxy radicals have the potential to damage cellular lipids, nucleic acids, proteins and carbohydrates leading to impairment of cellular function and integrity. The rate of free radical production must overwhelm the cyto-protective defense of cells before injury occurs⁽¹⁵⁾

Iron may induce Oxidative stress (OS) via production of reactive oxygen species (ROS) facilitating mammary carcinogenesis. The role of iron in relation to OS is a potential risk factor in the development of breast cancer⁽¹⁶⁾

Excess iron is also an etiological factor for development of breast cancer as iron is well known for catalyzing Fenton/Haber-weiss or auto oxidation reactions, that can lead to the formation of reactive oxygen species(ROS) and lipid peroxidation, as well as their products which give rise to mutagenic aldehydes, such as 4- hydroxyl nonenal and in conjunction with oestrogen in breast can catalyse redox cycling of catechol oestrogen metabolites quinone and semiquinone, which generates ROS which act as secondary messengers in intracellular signaling cascades which can maintain oncogenic phenotype of cancer cells.^(17,18)

The distribution of ferritin levels was found to be significantly higher postmenopausal patients as compared to controls with Mean \pm SD=204.19 \pm 117.24 and Mean Rank=67.25 and as compared to controls with Mean \pm SD=84.35 \pm 25.80 and mean rank=33.75 and Man Whitney U=412.50 and p value<0.05.

It was suggested that elevated serum ferritin might indicate the presence of malignant disease and could be regarded as the predictor of positive lymph node involvement in patients

with breast cancer prior to surgery. These values were significantly higher compared to healthy persons as well in breast cancer patients in early stages of disease in comparison to advance cases (p<0.05)⁽²⁴⁾

In study conducted by Harshal P Narkhede 2014 revealed statistically highly significant rise in serum ferritin levels in Breast cancer patients mean \pm SD 235 \pm 10ng/ml than normal healthy controls mean \pm SD 101 \pm 7ng/ml. Breast cancer patients of all three age groups viz 25-40, 41-55 and 56-75 years exhibited higher serum ferritin levels than three respective age groups of controls. Breast cancer cases between 56-75 years of age exhibited statistically significant p<0.05 rise in serum ferritin than controls of same age. 25-40 and 41-55 years sub groups cases had highly significant rise of serum ferritin than their respective controls with p<0.001.⁽²⁵⁾

In a study conducted by Harshal Narkhede, 2013... higher serum ferritin levels were observed in breast cancer patients than normal healthy controls. The difference was found to be statistically significant (p<0.01). Besides higher serum ferritin levels were found in cases lymph node involvement as compared to those in cases without lymph node involvement. The difference was statistically significant. (p<0.001)⁽²⁶⁾

In a study conducted by Rakesh Dhankar, 2014... the rise in ferritin levels were reported significantly more in advanced stage as compared to early stage carcinoma (p<0.001) and high ferritin levels were associated with advanced malignant phenotype and significantly higher as compared to group with less advanced stage. (p<0.001)⁽²⁷⁾

CONCLUSION

In premenopausal patients iron was found to be significantly lower in breast cancer patients indicating the role of low iron in the process of carcinogenesis as low iron increases several pro-angiogenic factors like VEGF and Basic fibroblast growth factor and anti-angiogenic (e.g. thrombospondin 1) produced by both tumor cells and stroma which increases risk of cancer and ferritin was also found to be lower in premenopausal patients as compared to controls as it is iron storage protein. But in case of postmenopausal women both iron and ferritin was found to be significantly higher in patients as compared to controls. Since high iron leads to increase in oxidative stress through generation of free radicals via Fentons/ Haberweiss reaction which have potential to damage cellular lipids, nucleic acids, proteins and carbohydrates leading to the impairment of cellular function and integrity and increased oxidative stress is a potential risk factor in the development of breast cancer. Thus this study indicates that iron acts as a double-edged sword having role in carcinogenesis both in low and high concentrations.

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Source of support: Nil

Conflict of interest: None declared

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