Serum Iron And Ferritin As Diagnostic Marker of Breast Cancer

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Abstract: Background: It is the most frequently diagnosed cancer in women worldwide affecting. Risk of cancer increase with the age and it is higher in postmenopausal women. Iron deficiency anaemia is most prevalent in Indian women population. Association of serum iron profile and ferritin could be breakthrough for breast cancer detection and could become a future tumour marker. The aim of present study was to measure the serum ferritin, iron, total iron binding capacity and unbound iron binding capacity concentration in breast cancer patients to find out role of serum biochemical parameters (ferritin, iron, UIBC and TIBC) as biomarkers for diagnosis of breast cancer. Method: Total 100 cases were analysed during a period of 3 years they were histopathologically diagnosed breast cancer patients and age matched 100 healthy controls were taken . Levels of serum trace elements were estimated by colorimetric method SPSS version 17 were used for statistical confirmations. Result: Patients when compared to controls, Serum iron (124.87±39.12)and TIBC (318.5 ±62.97) were significantly lower and serum ferritin (188.93 ± 64.46) is significantly higher ($p<0.001$)in breast cancer patients and these parameters shows a significant positive correlation with tumour marker CA15-3. Conclusion: Based on findings our study concluded that breast tumours can cause increase serum level of iron ,ferritin and TIBC in female breast cancers patients and suggest that all these biochemical parameters can be used as a diagnostic marker for the follow-up of these breast cancer patients.
[A Vamne, Natl J Integr Res Med, 2018; 9(1):1-6]

Key Words: Breast cancer, ferritin, iron, diagnostic marker

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Introduction: 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). It is the fifth most common cause of death from cancer in women, breast cancer is more common after menopause.[1].Cancer of breast with estimated 1.5 lakh new cases during 2016 in India.[2]According to the National Cancer Registry, breast cancer accounts for 27 per cent of all cancers in women, with one in every 28 women likely to develop it during her lifetime, so the burden of breast cancer on the healthcare is increased, because of this the need for cost-effective methods of early detection, screening and surveillance is imperative.

The iron metabolism is another pathway potentially linked with carcinogenesis. Iron plays a fundamental role in important biological processes in eukaryotic cells such as oxygen transport, cellular respiration, and redox reactions; consequently iron homeostasis is precisely regulated. Most circulating iron is bound to transferrin; the rest of iron is either serum-free iron or iron stored in cells bound to ferritin. Total iron-binding capacity (TIBC) measures the ability of plasma proteins to bind iron and reflects the fraction of transferring-free places to bound iron, meaning that low values of TIBC evidence transferrin saturation (TSAT) and consequently high iron stores in cells[3].

Different mechanisms of iron involvement in carcinogenesis have been suggested, including oxidative DNA damage by iron-catalysed free radical production, alterations in gene expression consistent with increased iron requirements in proliferating cells, as well as decreased immune surveillance against cancer [4]. Excess iron has been shown to promote protein and genomic alterations mirrored in human cancers[5] and this may occur via iron-induced persistent oxidative stress[5]. Moreover, iron sequestration machinery is activated by inflammatory processes associated with chronic diseases such as breast cancer for which cancer-associated anaemia is being broadly studied[6]. Deficiency or excess of iron can lead to multiple organ failures and in extreme cases to death. The latest studies show that the iron can significantly influence the risk of cancer development and progression. Scientists reported association between high levels of iron in the serum and the risk of colon, liver, stomach and breast cancers[7].

Ferritin has been traditionally considered a cytoplasm iron storage protein. However, several studies over the last two decades have reported the nuclear localization of ferritin, specifically H-ferritin, in developing neurons, hepatocytes, corneal epithelial cells and some cancer cells. This ferritin beyond iron

storage, such as a role component, DNA protection form iron - induced oxidative damage, and transcription at regulation [8].

The levels of ferritin are also found to be raised in malignancies. The reason for high levels of ferritin is unclear. It may be due to expression of a tumor derived protein which interferes with iron metabolism or due to nonspecific effect of malignancy on reticulo-endothelial iron metabolism as seen in breast cancer patients[9]. It may also be due to inappropriate ferritin synthesis by mononuclear phagocytic cells[10]. Secretion of ferritin is stimulated by cytokines. Cytokines play an important role in causation of cancer and ferritin plays a prominent role in cytokine response[11]. Thus, iron, ferritin and tranferrin are significantly associated with carcinogenesis, more so, with carcinoma breast. Not many studies are available in literature to comment on levels of serum iron along with its storage form ferritin and binding capacity of iron TIBC in patients of breast cancer. The laboratory estimation of these iron profile markers may have a diagnostic significance in breast carcinoma.

Objectives:

1) To evaluate the variation of serum ferritin level with healthy women and those with breast carcinoma.
2) To evaluate the variation of serum iron level with healthy women and those with breast carcinoma.
3) To evaluate the variation of serum UIBC and TIBC level with healthy women and those with breast carcinoma.
4) To assess the correlation between tumour marker CA15-3 and these metabolic parameters.
5) To establish the relationship between above parameters in breast cancer.

Method: This study was conducted in department of medical biochemistry, index medical college, hospital and research center and MGM medical college its associated MY hospital , from 2014 to 2016, On approval from ethical committee, 100 histopathologically proven breast cancer cases were analysed in our study and they were compare 100 healthy age matched females controls . Seven ml of venous blood was withdrawn from each individual using disposable syringes in blue vial. The samples were immediately centrifuged for 10 min at 3000 rpm, the serum obtained was removed and kept at -20c• till analysis. Biochemical parameters were done by fully automatic biochemistry analyser.

Exclusion criteria: For Cases group, subjects having benign breast tumour or with mass anywhere else in the body; those who have ever received treatment for breast cancer in any form like surgery, hormones, radiotherapy or chemotherapy; patients with history of liver or kidney impairment, acute inflammatory and infectious diseases, anaemia (Hbless than 10g%), diabetes and those on medications like iron supplements, OC pills, steroids or thyroxin, etc. were excluded from the study, as any of these factors may affect serum ferritin . For Control group, subjects with BMI >30 Kg/m2 , fasting plasma glucose >100 mg/dl, blood pressure >130/85 mm Hg and central obesity were excluded from the study.. Also, controls satisfying the International Diabetes Federation (IDF 2006) diagnostic criteria8 for Metabolic Syndrome were excluded from study.

Statistical analysis: Data were computed and analysed using Statistical Package for Social Science (IBM SPSS version 20.0) computer software. Student t-test, Pearson correlation analysis and One-way ANOVA were used. P. value at 0.05 was considered statistically significant.

Result: In our study I was include 100 cases and 100 healthy control in which, serum iron in healthy control is 100.04 ±20.7 µg/dl and in breast cancer patient (BC) is 124.87±39.12 µg/dl. Serum iron level were significantly high in breast cancer patient ($p<0.001$) and. Serum ferritin level is significantly high in breast cancer patient ($p<0.001$) Serum TIBC were significantly increased ($P < 0.05$) in breast cancer .Serum UIBC heaving no significant relationship between cases and healthy control. (Table 1)

Table 1: Comparison of Serum biochemical parameters in healthy control and breast cancer patients

Parameters	Female Control (100)	Breast Cancer(100)	P Value
	MEAN±SD	MEAN ±SD	
S Iron	100.04±20.7	124.87±39.12	< 0.001
S. Ferritin	103.15± 34.40	188.93 ±64.46	< 0.001
S. Uibc	201.80±29.6	193.78 ±44.55	NS
S.Tibc	301.85± 35.08	318.5 ±62.97	< 0.05

Pearson correlation analysis between CA15-3 and variables of interest breast cancer cases in showed that serum CA15-3 was significantly (P > 0.001) positively associated with serum iron (r=0.85), ferritin (r=0.26), TIBC (r=0.55). No significant correlation found with UIBC (Table 2).

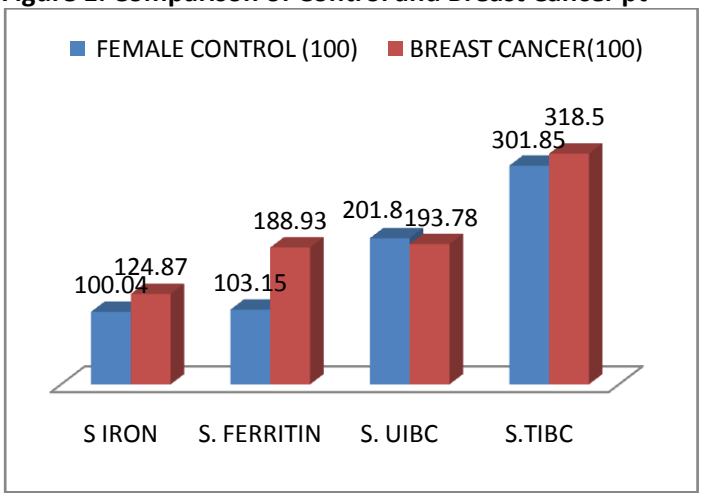
Table No 2: Correlation of tumour marker CA15-3 with biochemical parameters in breast cancer patients.

Biochemical Parameters	R- Value	P- Value
Serum Iron	0.85	<0.001
Serum Ferritin	0.26	<0.001
Serum Uibc	0.08	Ns
Serum Tibc	0.55	<0.001

Discussion: Overall, we found the levels of iron, ferritin and TIBC were found to be significantly increased in patients of breast cancer as compared to healthy controls (p<0.001).Breast cancer is estrogen dependent and increased estrogen exposure is found to be linked to raised serum iron levels[12,13].

J. Crosset al found similarly increased ferritin levels which will be associated with risk of breast cancer in literature and this may be due to increased expression of a particular protein in tumor cells which may interfere with iron metabolism or cancer may produce some non-specific effect on iron metabolism in reticulo-endothelial cells.

Figure 1: Comparison of Control and Breast Cancer pt



The levels of ferritin correlate with severity too, as significantly higher levels were observed in advanced stage as compared to those in early stage. Higher TIBC is reported to be associated with increased risk of malignancies like colon cancer[14] but reports in breast cancer are sparse in literature. Besides playing important role in iron metabolism, ferritin and transferrin are considered acute phase reactants with reciprocal roles Wish[15]. As they could not observe the inverse relationship between these two parameters, their predominant role, here, may be related to iron metabolism only. The increased levels of TIBC, which is a measure of transferrin, and ferritin, might be a reflection of impairment in iron metabolism seen in breast carcinoma (Figure 2,3)

Figure 2: Correlation of CA 15-3 with S. iron level

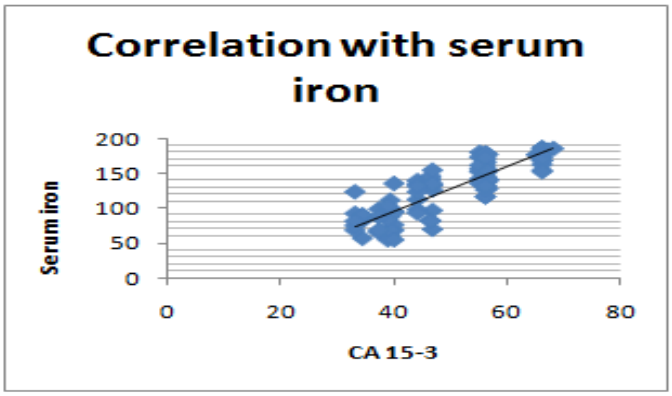
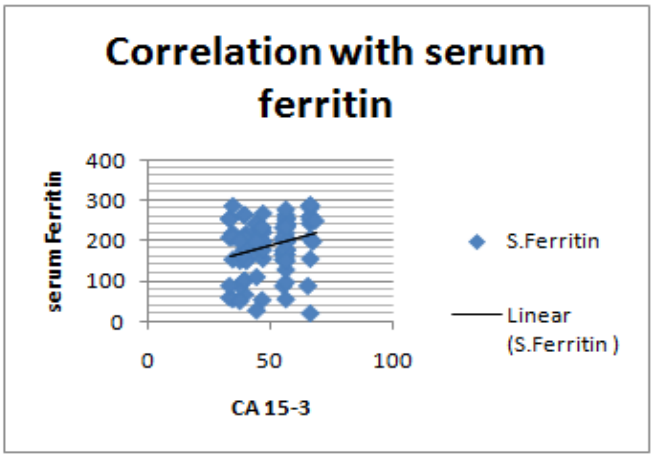


Figure 3: Correlation of CA 15-3 with S.ferritin level



Rufaida Mustafa Ahmed Mustafa et al in their study on 120females, 50 cases with breast cancer and 70 breast cancer controls were found statistically significant increase in the mean of serum iron and decrease in transferring saturation percent in women with breast cancer while no significant variation in the mean of TIBC between case and control groups[16]. The finding of Pavithra et al in their study is similar to this study in serum iron level; they found significantly high level so serumferritin54femalepatients with breast cancer when compared to 54 female controls[17].

Rakesh Dhankhar et al found the levels of iron, ferritin and TIBC were significantly increased in patients of breast cancer as compared to healthy controls ($p<0.001$). The levels were found to be higher in group III as compared to group II patients, though the difference was statistically significant in levels of ferritin and iron only[18].BasimaSadiq Ahmed etal found that the activity of serum ferritin is consistently higher in breast tumor[19].

Figure 4: Correlation of CA 15-3 with TIBC level

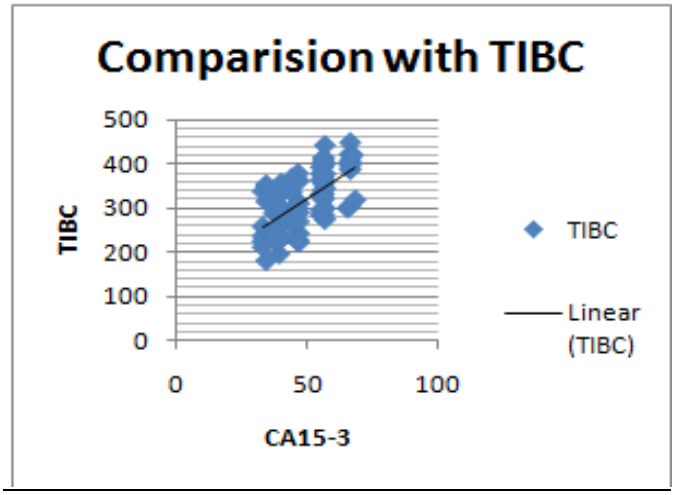
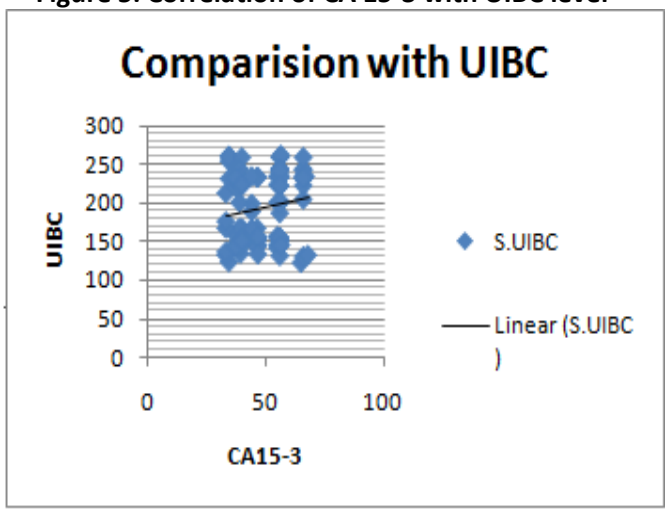


Figure 5: Correlation of CA 15-3 with UIBC level



Sandhya Mishraet al study includes 102 confirmed cases of carcinoma breast with and without metastasis and 25 healthy non-pregnant females. A significant increase ($p<0.001$) was observed in ferritin, LDH and GSH levels in cancer patients without metastasis in comparison to normal control subjects. Patients with metastasis had further elevated ($p<0.001$) levels of Ferritin, ALP and GGT as compared to non-metastatic patients[20].

Harshal P. Narkhedeetal study revealed overall significant rise of serum ferritin level in breast cancer subjects than in control subjects[21]. Similar findings noted by Kher et al.[22] and Ulbrich et al.[23] Moore et al have also reported rise in serum ferritin level among breast cancer subjects and they have attributed this rise to be the cause of tumourigenesis as ferritin may act as source of free iron[24].

Elevated serum ferritin may be the cause of carcinogenesis in breast owing to the release of free iron as the triggering factor for free radical induced carcinogenesis[25].BaeYJ et al have suggested raised serum iron to be a risk factor for carcinogenesis in breast tissue[26].

Ferritin acts as a source of this free (functional) iron which triggers oxygen-reactive species generation through redox cycling of oestrogen and various oestrogen metabolites. Free radicals produced as a result of this reaction have been considered to cause peroxidation of cellular membranous bio-molecules and DNA damage. The resultant chromatin and DNA damage in the form of DNA adducts, DNA breaks and activation of oncogenes induce tumorigenesis.

In view of overall raised serum ferritin levels among cases in this study, the possible role of iron in breast carcinogenesis cannot be underrated. The same can be explained by the demonstration of role of iron in induction of carcinogenesis by Wyllie S et al.[27] and Ebina Y et al.[28] They have confirmed the induction of carcinogenesis in hamsters supplemented with iron and oestrogen in their two separate experiments. Wyllie S et al have also demonstrated the mobilisation of iron (in ferrous form) out of ferritin during conversion of catecho l- oestrogen to its quinone derivatives in vitro[27].

Maira Mahmoud, et al reported that the mean serum ferritin was significantly higher in breast cancer patients when compared with controls. Besides, a highly significant difference was observed when mean serum ferritin values were compared in each of the four stages i.e. stage I , stage II , stage III & stage IV of breast cancer with controls[29]. Some studies report a significant difference between serum ferritin levels and advancing breast cancer stages[30-33].

Thus it seems likely that alterations in , serum ferritin and CA 15-3 levels are characteristics of patients with breast cancer. Based on the results of the current study it is recommended that serum Ferritin may be used as diagnostic as well as prognostic markers for BRCA. CA 15-3 along with Carcinoembryonic Antigen (CEA) are no doubt the most reliable and acceptable tumour markers for breast cancer patients. However, the analytical method of these advanced tumour markers are not only expensive, but unapproachable for general population, as the facilities for these are available only at sophisticated and well-equipped centers with latest technology.

Conclusion: Thus, it may be concluded that iron metabolism is strongly involved in pathogenesis of carcinoma breast and may help in assessing severity and diagnosis of the disease. In spite of its limitations, this study concluded that there is a statistically significant difference in serum iron, ferritin and TIBC (increased) in females newly diagnosed with breast cancer and apparently healthy females and all these three biochemical parameters were show significant positive association with tumour marker CA15-3.Based on findings our study concluded that breast tumours can cause increase level ofiron ,ferritin and TIBC in female breast cancers patients and suggest that all these trace elements can be used as a diagnostic marker for breast cancer patients.

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Conflict of interest: None
Funding: None
Cite this Article as: Amrita V, P Sarkar, K sodavadia. Serum Iron And Ferritin As Diagnostic Marker of Breast Cancer. Natl J Integr Res Med 2018; 9(1):1-6