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Original Article

Prognostic Significance of Cellular Iron Metabolism in Breast Cancer

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ABSTRACT

Cancer is caused due to rapid and uncontrolled growth of cells. Among females, one of the most prevalent types of cancer globally is breast cancer. Potential risk factors for rising breast cancer are family history and estrogens. Radiation exposure, alcohol use, tobacco smoking, age, and race are other risk factors for developing breast cancer. **Objective:** Current study was aimed to check iron expression in the biopsies of patients with different grades of breast cancer and to see the prognostic significance of cellular iron metabolism in breast cancer. **Methods:** A total of 24 breast biopsies were studied using a cross-sectional study design, among which 19 cases were poorly differentiated, 5 cases were moderately differentiated and there was no case of well-differentiated breast carcinoma. A total of 24 biopsies were taken between ages 20 to 80 years and all patients were females. **Results**: Among the 5 moderately differentiated cases,2 cases (40%) were positive for iron staining, and among 19 poorly differentiated cases, 8 cases (42%) were positive for iron staining. patients between age group 41-80 were more iron positive. **Conclusion:** It has been concluded that iron plays a significant role in the development of breast cancer. Both excess and deficient iron levels can potentially affect the prognosis of breast cancer.

INTRODUCTION

When a cell starts to develop rapidly and multiplies again and again until it forms a lump, it is called cancer or malignant tumor [1]. Cancer is an umbrella term for atypical growth of cells or proliferation of cells (un control growth [2]. Some genes undergo mutation and are transformed into genes that promote cancer growth. These genes are known as “Oncogenes” [3]. Tumors may be malignant or benign. Cancer is the malignant tumor which starts from one abnormal cell and goes on increasing compounded [4]. In all other types of cancers, breast cancer is the most common type of malignancy [5,6]. Breast cancer is the 2nd principal cause of cancer related female deaths and develops from ductal or lobular epithelium [7]. Earlier diagnosis can improve the survival rate in the breast cancer patients.[8] Breast cancer spreads initially via lymphatic vessels to the lymph nodes in the armpit. If the cancer cells not stopped there than they continue travelling in the lymphatic to other parts of the breast [9,10]. Breast cancer usually occurs due to cell multiplication under the influence of estrogen and infringing on other tissue which spreads to other regions of the body [11,12]. C-reactive protein (CRP), which are acute-phase proteins, are considered a extrapolative marker of inflammation and their serum levels are elevated in patients with breast carcinomas [13]. Clear evidence has been found regarding the involvement of soluble and cell-bound iron-binding protein Ferritin (FTN) and Transferrin (TRF) in breast inflammation and cancer [14]. Iron being an effective pro-oxidant, may increase the risk of breast cancer. The amount of iron stored in the body in the form of iron stores increases the risk of breast cancer [15]. Iron deficiency because of menstruation and iron accumulation due to the cessation of menstruation has a considerable impact on breast cancer. Increased levels of iron elevate oxidative stress and maintain mutagen-activated protein kinase activation, which is significant in breast cancer advancement. A proangiogenic environment stimulated by an iron deficiency can result in an increased occurrence of breast cancer in adolescent women and pro-oxidant conditions

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which are consequences of iron-accumulation can direct towards towering rates of breast cancer in aged women [16]. Copious amounts of ferritin, a primary intracellular iron storage protein, are found in the blood circulation of breast cancer patients. Elevated levels of both serum and tumor ferritin are obtained in the biochemical analysis of these patients. Low amounts of ferritin were found in cancer cells but contrarily, increased penetration of ferritin-rich CD68-positive macrophages was seen in increased tumor histological grade. Ferritin stimulated the production of the epithelial breast cancer cell. Moreover, this proliferative effect has an impact on the iron concentration of ferritin and did not increase intracellular iron levels in cancer cells. As the penetrating macrophages release ferritin in breast tumors, spiking ferritin levels within tumor cells may signal towards the inflammatory effector's mechanism which was opted by the ferritin for directly stimulating tumorigenesis [17]. Systemic iron is regulated by two proteins i.e. ferroprotein and hepcidin. Ferroprotein is involved in the export of intracellular non-heme-associated iron and is regulated by the hormone hepcidin. High ferroprotein and low hepcidin gene expression is identified as an extremely favorable cohort of breast cancer patients. Therefore, ferroprotein protein is seen as a strong and independent predictor of prognosis in breast cancer [18]. Iron metabolism is disrupted in breast cancer. Iron initiates breast tumor growth and metastases. Tumor formation in breast is initiated by iron through the promotion of redox cycling of estrogen metabolites. Breast cancer cells acquire and retain excess iron by up regulation of iron import and down regulation of iron export. Breast tumor growth may also foster due to changes in iron metabolism within macrophages and other cells belonging to the tumor microenvironment. In breast tumor expression of iron, a metabolic gene can be used as a predictive factor for breast cancer tumors [19].

METHODS

Overall, a cross-sectional study related to breast biopsy samples, consisting of 24 cases of breast cell carcinoma was conducted on patients with breast cancer who visited the Fatima Memorial Hospital, Ittefaq hospital, and Mayo hospital Lahore. All patients were females aged between 20 to 80 years with a confirmed diagnosis of breast carcinoma. Patients with incomplete history were not included. Data from the patients was collected through a Performa. Tissue submitted for histopathology were not more than 3mm in thickness and not larger than the diameter of slides used. Most specimens from solid tissues were cut in the form of pieces measuring 10-15mm on the slides and 2-3mm in thickness.

RESULTS

Biopsies of 24 breast cancer patients were studied in this research. Cases were divided into three groups based on the Histopathological findings i-e well differentiated breast carcinoma (no case), moderately differentiated breast carcinoma (5 cases) and poorly differentiated breast carcinoma (19 cases) (Table 1, Figure 1).

Well	0	0	0
Poor	8/42	11	19
Moderate	2/ 40	3	5
Total	10/42	14	24

Table 1: Iron expression in studied cases

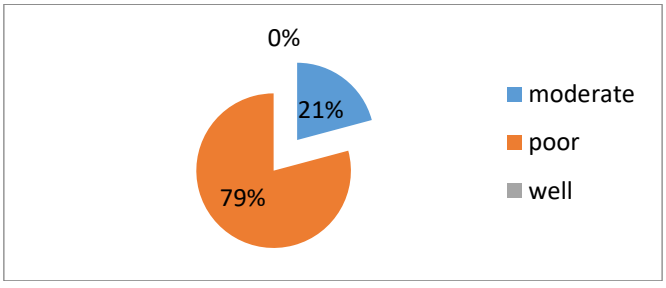

Figure 1: Pie chart indicating the Grading of breast cancer cases

The pie chart is indicating that the poor grade is 79%, moderate is 21% and well is 0%. In the studied biopsies, poor grade was common. The cases of well differentiated were not found because early diagnosis in breast cancer is rarely found and in early cases the biopsies are not done (Figure 1).

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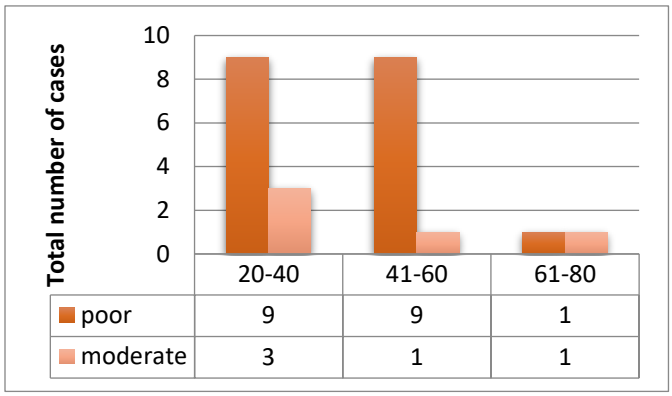

Figure 2: Grade with respect to age

In **figure 2**, the common age group was 20 to 40 and 41 to 60. Poor grade was most common in these age groups. Moderate grade was common in age group between 20-40 years. Few cases were observed within the age group of 61-80. Whereas, moderate grade cases were less frequent in the age group of 41 to 60 and 61 to 80. In figure 3, iron expression is shown in grades. 24 biopsies were studied in which 10 were iron positive and 14 were iron negative. For iron positivity, 8 cases were of poor and 2 were of moderate grade. For iron negativity, 11 were of poor and 3 were of moderate grade. And in well grade no cases were found.

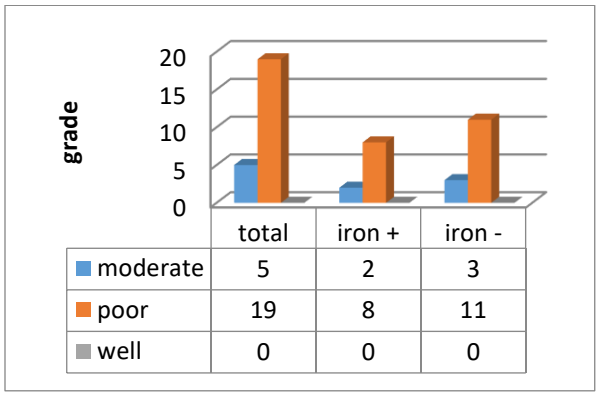

Figure 3: Iron expression in grades

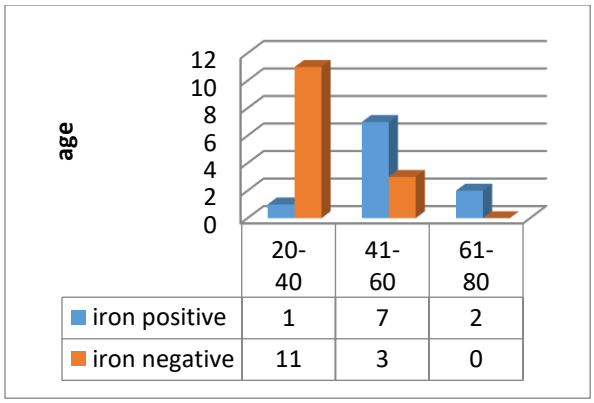

Figure 4: Iron expression with respect to age

Iron positivity is commonly seen at the age group of 41-60 and 61-80. Less commonly seen within the 20-40 age group. Iron negativity is commonly seen at age 20-40 and moderately seen at age 41-60.Iron negativity is not seen between age 61-80 (Figure 4).

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DISCUSSION

Breast cancer is one of the general malignancies and second leading cause of cancer related mortalities in females. Iron is an exceedingly important nutrient of the human body that has the ability to proceed the formation of free radicals and helps in the process of redox cycling with many different roles in metastasis and in microenvironment. Reprogramming of iron metabolism is a central aspect of tumor cell survival because pathways of iron storage, efflux, regulation & acquisition are all agitated in cancer. This role of iron has been discussed in a study carried out by Torti and Torti in 2013 [20]. In another study performed by Ye C *et al* in 2007, it was seen that iron stimulated progression of breast cancer. Ferritin, being the primary iron storage protein, is found profusely in blood circulation. High serum and tumor levels are found in breast cancer patients. This study comprehensively examined the distribution of ferritin in normal and malignant breast tissue during different stages of tumor development. In cancer cells ferritin expression is decreased but increased infiltration of ferritin rich CD-68 positive macrophages was observed with increased tumor histological grades [21].

CONCLUSIONS

It is concluded that iron is included in the list of risk factors associated with breast cancer and it has also been proved that iron plays a role in the development of breast cancer. By maintaining a check on the iron levels, increased prevalence of breast cancer can be prevented.

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