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Serum Copper Levels In Different Stages Of Breast Cancer.

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ABSTRACT

Copper plays an important role in inflammation and tumors. Breast tumor cells can readily take up copper from the blood. Copper is an important angiogenic factor for tumors. The present study was undertaken to determine the serum levels of copper in different stages of breast cancer and to compare with normal individuals. 99 participants (30 women healthy females as controls and 69 women with histologically proven breast cancer as cases) were included in the study after obtaining written informed consent. Total serum copper levels were determined in different stages of cancer from early to advance. SPSS 20.0 was used for statistical analysis. Data were analyzed by Student't' test. P-value less than 0.05 were considered significant. Copper levels were significantly increased ($p<0.0001$) as the disease progressed from stage 1 to stage 3 advanced breast cancer in postmenopausal women. Lowering Copper in diet of breast cancer patients may also be useful in delaying the progress of the disease and making treatment more effective.

Keywords: Serum Copper, Breast Cancer.

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INTRODUCTION

Breast cancer is the commonest cancer among women in the world and the incidence is rising even in developing countries like India [1]. Several causative factors are attributed to the occurrence of breast cancer and several serum markers have been identified. In humans, copper is essential for proper functioning of organs and metabolic processes [2]. The human body has the ability to ensure a constant supply of copper while eliminating excess copper. Humans are exposed to copper and copper containing compounds by various routes [3]. Earlier studies reported that Copper plays an important role in inflammation and tumors [4-6]. High copper levels have been found in many types of human cancers, including prostate, breast, colon, lung, and brain [7]. Copper concentration in serum and tumor tissue is higher than normal subjects [8-10]. Tumor cells seem to readily take up copper from ceruloplasmin fractions of plasma [11]. Copper also seems to be an important angiogenic factor for tumors [12]. Numerous molecules important to angiogenesis regulation have been shown to be either directly or indirectly influenced by copper levels the body [13]. It was reported that copper levels could be used as a prognostic factor in breast cancer. However, very few studies have shown the association between serum levels of Copper in various stages of breast cancer along with menopausal status, especially in India. The aim of the present study was to measure the levels of copper in normal subjects and in women in different stages of breast cancer and menopausal status.

MATERIAL AND METHODS

Participants and controls

69 cases of had histologically confirmed breast cancer and in different stages (stage 1 to stage 3) and 30 age matched healthy (controls) of females were included in the present study by convenient sampling after obtaining voluntary, free, written informed consent.

Research design:

Cross-sectional study

Methods

The serum was collected from these women to measure the levels of **copper by colorimeter method** by adding a specific color reagent and absorbance measured. The intensity of color is directly proportional to the amount of copper in the sample. The normal serum total copper ranges between 80 to 155 ug/dl.

Ethical consideration

The present study was approved by institutional ethical committee of M.N.J Institute of Oncology and Regional Cancer Centre, Hyderabad, Telangana.

Statistical analysis

SPSS 20.0 was used for statistical analysis. Data were analyzed by Student't' test. P-value less than 0.05 were considered significant.

RESULTS

Results were presented in table no 1 to table no 3 and figure no 1 to figure no 2. It was observed that age is an independent risk factor for breast cancer. There may be a general mineral nutritional deficiency in postmenopausal women leading to low levels of serum copper in them when compared to premenopausal controls. Gradual increase in copper levels was observed in both premenopausal and postmenopausal women with increasing stage of breast cancer. Mean Serum Copper levels of premenopausal controls and cases were close with p=0.54 which was not significant. However, there was a gradual increase in the levels of copper even in premenopausal women from early to advanced stages of breast cancer. This shows that there is some relationship between serum levels of copper and stage of breast cancer in premenopausal women. Mean

serum Copper levels in postmenopausal women were found to be significantly higher in breast cancer patients when compared to controls. The increase was found to be statistically significant with p<0.0001. This shows that there is a clear relationship between Copper levels and stage of breast cancer with higher levels in advanced breast cancer cases. In our study, serum copper level was found to be higher in stage 3 of breast cancer. The levels were more in postmenopausal stage 3 cancer than premenopausal stage 3.

Table 1: Mean age of controls and cases

Menopausal status	Controls (n=30)	Cases (n=69)
Mean Age (Yrs) Premenopausal	29.87 (± 7.38)	39.76 (± 6.46)
Mean Age (Yrs) Postmenopausal	52.93 (± 7.08)	54.6 (± 9.06)

Data presented are Mean ± SD.

Table 2: Mean ages as seen in different stages of breast cancer

Menopausal status	Controls	Cases Stage 1	Cases Stage 2	Cases Stage 3
Mean Age (Yrs) Premenopausal	29.87 (± 7.38)	39.8 (± 4.15)	38.14 (± 8.11)	40.57 (± 6.51)
Mean Age (Yrs) Postmenopausal	52.93 (± 7.08)	52 (± 5.98)	56 (± 10.66)	55 (± 9.33)

Data presented are Mean ± SD.

Table 3: Total serum copper levels in controls and cases

Menopausal status	Controls Cu (µg/dl)	Cases Stage 1 Cu (µg/dl)	Cases Stage 2 Cu (µg/dl)	Cases Stage 3 Cu (µg/dl)
Premenopausal	130.25 (± 41.13)	114.66 (± 46.55)	122.02 (± 53.64)	143.67 (±49.9)
Postmenopausal	113.53 (± 33.84)	119.01 (± 35.39)	131.62 (± 86.78)	156.11 (± 62.85)

Data presented are Mean ± SD.

Figure 1: Premenopausal women and Serum Copper levels – Controls and Cases

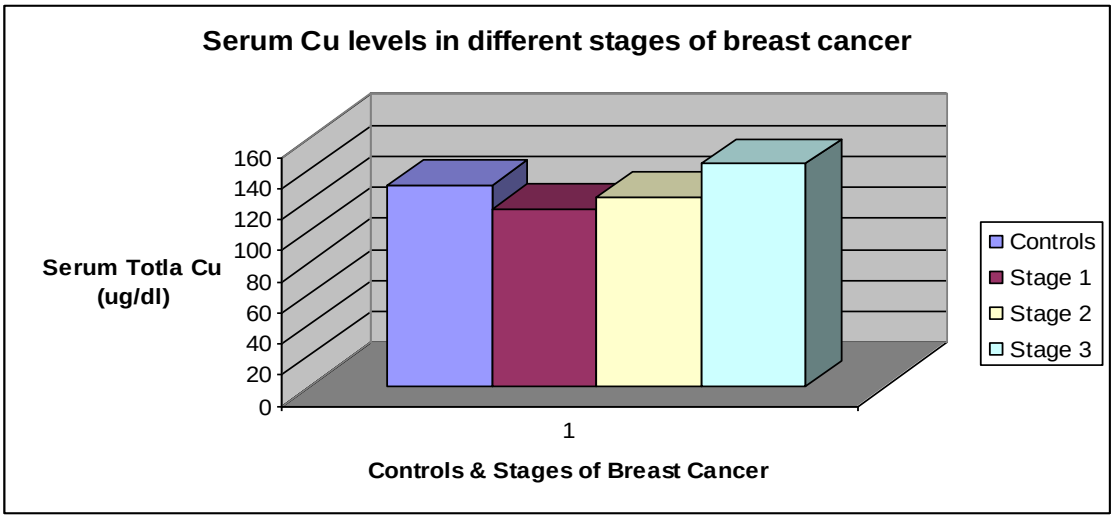

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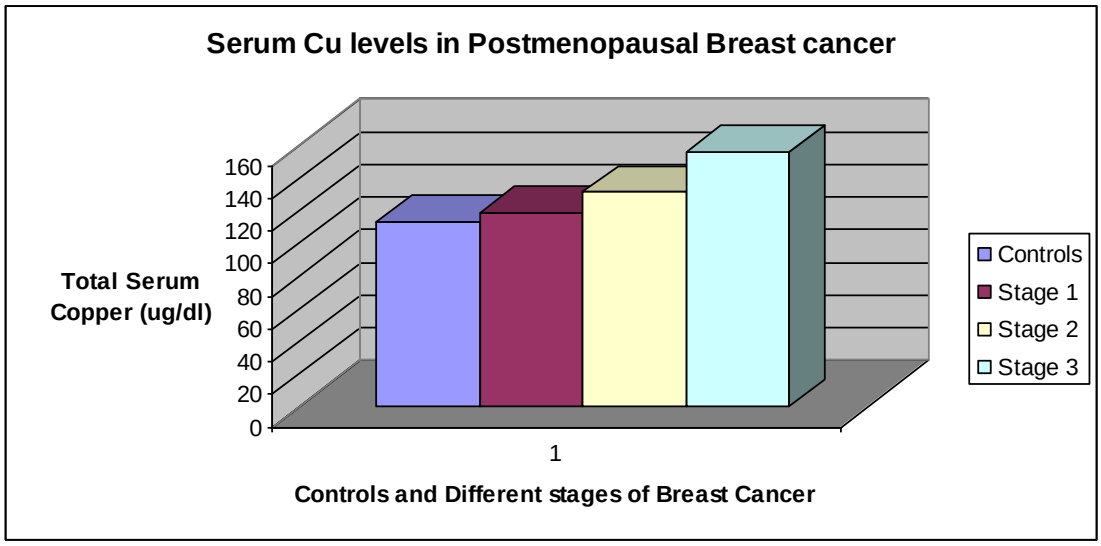
Figure 2: Postmenopausal Copper levels in controls and cases



DISCUSSION

In the present study, it was observed that copper levels are elevated with increasing stage of breast cancer both in premenopausal and postmenopausal women. The increase is more significant in postmenopausal women indicating that the pathogenesis maybe different in the two groups. Also, it is seen from table 3 that the levels of serum copper are highest in stage 3 of breast cancer and is even more in postmenopausal cases than premenopausal cases. This shows that copper plays a more positive role in advanced stages of cancer as more number of tumor cells are available to take up copper. High levels of copper determine angiogenesis and several molecules important for angiogenesis regulation are influenced by copper levels in the body [14]. Copper has been shown to induce endothelial cell migration which is an essential early step in angiogenesis and copper binding cells become angiogenic when bound to copper [15,16]. Levels of copper are elevated with advancing cancer in our study which is in accordance with studies done earlier [17]. Tumors which become angiogenic exhibit high metastatic potential with high mortality rates [17]. Also high levels of copper hinder treatment with chemotherapeutic agents as evidenced by the fact that treating with Cu chelating agents like tetrahydromolybdenate have increased the efficacy of the drugs [18]. If copper levels are high or elevated in cancer patients, it results in decreased cisplatin uptake and increased resistance to this drug. Hence it is essential to know the levels of copper in breast cancer patients as Cisplatin is used for treatment of metastatic cancer of the breast [12]. The precise mechanism responsible for the alterations in trace element levels in breast cancer patients is still unclear and need further evaluation. However, serum Cu levels may be used as a biochemical marker in these patients. Copper levels needed for physiologic functions are lower than those favored by tumor angiogenesis. It is necessary to deplete Copper to a therapeutic level as shown in earlier studies [19]. This study would help in estimating that level.

Limitations

Major limitation in our study was less sample size. Measuring plasma ceruloplasmin might be a better indicator than total serum copper levels and is a good marker of body copper status [20].

CONCLUSION

Lowering Copper in diet of breast cancer patients may also be useful in delaying the progression of the disease and making treatment more effective.

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