

Research Article

Relationship between Trace Elements and Major Gynaecological Malignancies

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Abstract: Trace elements have long been identified to play key roles in cell metabolism and by extension malignant disease. Copper in particular has been shown to increase in different types of genital cancers, while Zinc levels are depleted. This study set out to evaluate the serum Copper and Zinc levels in patients with cervical, endometrial and ovarian cancers. A total of 40 patients were recruited, 16 each with cervical and ovarian cancer and 8 with endometrial cancer. These were matched with 40 controls from the Gynaecology clinic. The serum Copper levels were elevated in all types of genital cancers and statistically significant in cervical 0.65 ± 0.082 mg/L and endometrial cancers 0.54 ± 0.14 mg/L. The serum Zinc levels were reduced in all cancers, however non to a statistically proportional level. The Copper/Zinc ratio in cases was markedly elevated when compared to that of the controls (1.19). The results indicate a possible clinical relevance of accessing serum Copper levels in women with genital tract malignancies, particularly in cervical cancer. There may also be a role for serum Copper levels in monitoring disease progression in the management of genital malignancies.

Keywords: Cervical, copper, endometrial, ovarian cancer, Zinc

INTRODUCTION

Trace elements are known to play a pivotal role in the process of normal growth and differentiation of various tissues in animals and humans (Saha *et al.*, 1999). Their requirement for sustenance of tumor cell proliferation is hence considered to be of significant importance (Schwartz, 1975). Accumulation of free radicals has been implicated in the pathogenesis of many diseases including cancer (Zuo *et al.*, 2006). Zinc is one such essential element that prevents the formation of free radicals. In addition to its role as an anti-oxidant, zinc is also known to participate in nearly 120 reactions taking place in a living organism (Saha *et al.*, 1999). More recently, studies have shown that this element may also play an important regulatory role in initiation of cell-mediated immunity (Rink and Haase, 2007). Recent studies have demonstrated that Zinc deficiency seriously inhibited the development of lymphoid organs, impaired the progression of lymphocytes from the G0/G1 phase to the S phase and caused pathological injury in the lymphoid organs (Cui *et al.*, 2004).

Among the trace elements, significant changes have been observed for serum copper concentration in various malignant conditions. Cavallo *et al.* (1991) as a result serum copper concentration is considered as a non-specific marker for monitoring the progression of

malignant disease (Chakravarty *et al.*, 1994). As with other forms of gynecological cancers, the plasma level of copper and zinc is affected by the presence of endometrial cancer. The plasma copper level in patients with endometrial cancer has been shown to increase significantly while the zinc levels show a significant decrease (Yaman *et al.*, 2007). In a study done by Jafari Shobeiri *et al.* (2011) to determine the serum concentration of copper, zinc and ratio of copper/zinc in patient with ovarian cancer and those with benign ovarian lesion. They discovered a significant increase in mean serum levels of copper ($p < 0.001$) and the copper/zinc ratio ($p < 0.01$) in malignant group compared with the benign group.

The serum levels of copper and zinc in cervical cancer patient has been investigated by a good number of researchers. While some reported a significant increase in the serum copper level and a decrease in serum zinc level in patient with cervical cancer. Naidu *et al.* (2007), others reported that there was no change in the serum copper level and a decrease in the serum zinc level in patients with cervical cancer when compared to those without these diseases (Wong *et al.*, 1987).

This study set out to evaluate the levels of zinc and Copper in patients with cervical, Endometrial and Ovarian cancer.

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METHODOLOGY

This was a cohort study conducted at the department of Obstetrics and Gynaecology of the University of Benin Teaching Hospital.

The subjects were recently diagnosed cases of cervical, endometrial and ovarian cancer who had not had any treatment. The controls were patients in the Gynaecology clinic who did not have any malignancy. Presence of malignancy was an exclusion criteria.

Sample collection and analysis: Fasting blood samples were collected from the subjects after informed consent was obtained alongside administration of a questionnaire. Five millilitres (5 mLs) of venous blood was collected from the subjects' antecubital vein under aseptic condition using 5 mL sterile disposable syringe and needle and dispensed into an EDTA bottle. Blood was centrifuged at 3000 rpm for 10 min at room temperature. The separated plasma was placed into a plane tube and kept frozen until analyzed. Copper and zinc were estimated using atomic absorption spectrophotometer.

Statistical analysis: Data entry and analysis was done using the Statistical package for social sciences, SPSS (IBM SPSS statistic 16). Group mean was compared using ANOVA and the distribution of data was examined using the chi square and student's t-test as appropriate. A probability level of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 45 patients were recruited for the study, 3 patients declined to give consent, while 2 others had already completed a course of chemotherapy (6 cycles) and were excluded from the study. The cases were 40 in number, while 40 controls were matched with cases for age and parity.

The cases were made up of 16 patients with cervical cancer, 8 with endometrial cancer and 16 with ovarian cancer.

For patients with cervical cancer, the mean age was 47.6 years while their controls 48.2 years. The modal parity was 4. The mean serum copper level for the 16 cases was 0.65 ± 0.082 mg/L (0.4-1.03) and that of the controls was 0.31 ± 0.02 mg/L (0.14-0.57), this was statistically significant with $p < 0.05$. The serum zinc was 0.24 ± 0.04 mg/L (0.09-0.32) and that of the controls was 0.26 ± 0.03 mg/L (0.07-0.57) this was not statistically significant with $p > 0.05$ Table 1 and Fig. 1. The Copper/Zinc ratio for this group of patients was 2.7.

The mean age for patients with ovarian cancer was 58.7 years and their controls 55.1 years. The modal parity was 1. The mean serum copper level for the 8 patients was 0.48 ± 0.08 mg/L (0.19-0.69) and the controls 0.31 ± 0.02 mg/L (0.13-0.55) this was not statistically significant with $p > 0.05$. The serum zinc

Table 1: Copper and zinc levels of cervical cancer patients and controls

Trace elements	Cervical cancer (Mean±S.E.)	Controls (Mean±S.E.)	p-value
Cu (mg/L)	0.65 ± 0.082	0.31 ± 0.02	< 0.05
Zn (mg/L)	0.24 ± 0.04	0.26 ± 0.03	> 0.05

Table 2: Copper and zinc levels of endometrial cancer patients and controls

Trace elements	Endometrial cancer (Mean±S.E.)	Controls (Mean±S.E.)	p-value
Cu (Mg/L)	0.54 ± 0.14	0.31 ± 0.02	< 0.05
Zn (Mg/L)	0.17 ± 0.05	0.26 ± 0.03	> 0.05

Table 3: Copper and zinc levels in ovarian cancer patients and controls

Trace elements	Ovarian cancer (Mean±S.E.)	Controls (Mean±S.E.)	p-value
Cu (Mg/L)	0.48 ± 0.08	0.31 ± 0.02	> 0.05
Zn (Mg/L)	0.16 ± 0.01	0.26 ± 0.029	> 0.05

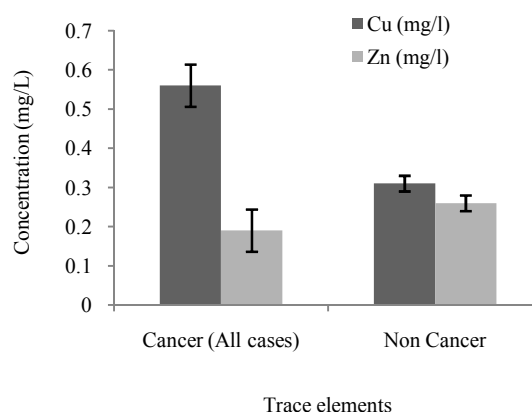


Fig. 1: Demonstrating the serum copper and zinc levels in all the cases and controls

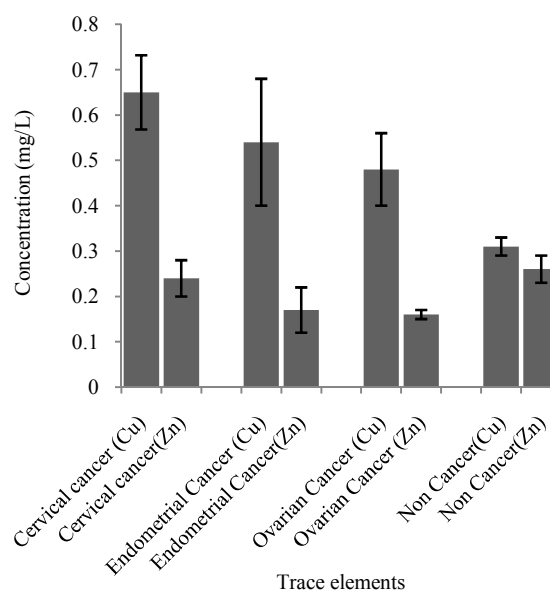


Fig. 2: Demonstrating the copper and zinc levels in cervical, endometrial and ovarian cancer's

level was 0.16 ± 0.01 mg/L (0.09-0.20) and the controls 0.26 ± 0.029 mg/L (0.06-0.56) this also was not statistically significant with $p > 0.05$ Table 3 and Fig. 2. The Copper/Zinc ratio for cases was 3.0.

The mean age for the endometrial cancer patients was 65.6 years while their controls had a mean age of 62.9 years. The modal parity was 2. The mean copper level was 0.54 ± 0.14 mg/L (0.12-0.76) while the controls had a mean copper of 0.31 ± 0.02 mg/L (0.13-0.56) this was statistically significant with $p < 0.05$. The mean serum zinc level was 0.17 ± 0.05 mg/L (0.02-0.27) and the controls 0.26 ± 0.03 mg/L (0.07-0.58) and this was not statistically significant Table 2 and Fig. 2. The Copper/Zinc ratio for cases was 3.17.

The Copper/ Zinc ratio in the controls was 1.19.

DISCUSSION

Reseachers are constantly developing better methods for diagnosing and prognosticating disease particularly in Oncology and one of the areas highly researched is trace elements, however most of the results have been contradictory. Yaman *et al.* (2007) zinc and Copper concentrations in serum and tissues have been extensively studied, particularly in cancer patients, but the precise role of these metals in carcinogenesis is not clearly understood (Yaman *et al.*, 2007). However one fact clearly stands out, that is, their levels are affected by malignant disease.

A lot of work has been done world-wide but studies from Nigeria are few or nonexistent. Copper has been identified as a possible non specific marker for diagnosis and prognosis in malignancies. Chakravarty *et al.* (1994) and that was one of the key findings in this study. In all of the cancer's investigated in this study, the serum Copper levels were higher than that of the controls by a statistically significant proportion, except in ovarian cancer where it was elevated by not statistically significant. In contrast to Copper, serum Zinc levels were reduced in all the cases however this was only statistically significant in cervical cancer cases. This ultimately resulted in an increase in the Copper/Zinc ratio which was 2.7, 3.0 and 3.1 for cervical, ovarian and endometrial cancers respectively. This result is similar to findings of numerous workers who have studied these trace elements. Naidu *et al.* (2007), Saxena *et al.* (2002), Kim *et al.* (2003), Chen *et al.* (1990) and Marinov *et al.* (2000). In all studies Copper has been found to be elevated and this may be as a result of mobilization of Copper from tissue to serum (Singh *et al.*, 1990). The addition of Copper to DNA in-vitro mediates more extensive damage to the bases of the DNA, thereby inducing mutations. It is believed that Copper may also elaborate other free radicals like Hydroxy ion resulting in the deactivation of certain tumour suppressor genes that can lead to initiation and/or progression of malignant disease

(Singh *et al.*, 1990). Zinc is a necessary ingredient for the growth of the cell and the integrity of the membrane, with rapidly proliferating cells in malignancies. Beerheide *et al.* (1999), this could result in depletion of serum Zinc levels in this category of patients, thereby explaining the reduced serum Zinc levels in all genital tract malignancies in this study.

The increase in the ratio of Copper to Zinc can be explained as an increase in serum Copper levels and a concomitant reduction in the serum Zinc levels. Some studies have also shown that with treatment of some cancers there is a corresponding reduction in serum Copper levels. Serum copper levels have also been evaluated with treatment and this has been shown to reduce as treatment is on-going (Chen *et al.*, 1990). In addition serum Copper levels increase with disease progression, (Kim *et al.*, 2003) discovered that the serum Copper levels increase proportionately in patients with pre-invasive cervical cancer when compared to those with invasive cancer.

It is therefore our conclusion that these results indicate a possible clinical relevance of accessing serum Copper levels in women with genital tract malignancies, particularly in cervical cancer. There may also be a role for serum Copper levels in monitoring disease progression and as a prognostic tool in the management of genital malignancies. There is a need to do more studies with a larger sample size.

The limitations of this study include the fact that the sample size is small, the stage of disease for the cases was not determined and patients were not categorized on the basis of the various subtypes of Gynaecological malignancies.

The authors wish to state that there was no conflict of interest in this study.

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