

## Evaluation of the Serum and Tissue Levels of Copper and Zinc in Patients with Gynecologic Tumors

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### Abstract

Serum and tissue copper (Cu) and zinc (Zn) levels were determined by atomic absorption spectrophotometry in 20 women with malignant gynecologic tumors and compared with levels in 15 with benign gynecologic tumors. A significant ( $p < 0.05$ ) elevation of serum copper levels in gynecological cancer patients when compared with those of benign diseases. Estimation of zinc level demonstrated a non statistically significant difference between malignant and benign gynecologic tumor patients. Determination of tissue copper and zinc contents revealed a significant ( $p < 0.005$ ) elevations of copper and non significant ( $p > 0.005$ ) decrease of zinc in malignant tissues with respect to those of benign tumors. In addition to it, there were essentially correlation between copper and zinc levels in serum and their levels in tissue in cancer patients but no such correlation in patients with benign tumors.

### الخلاصة

تم تقدير مستويات كل من مستويات النحاس (cu) والزنك (zn) بواسطة تقنية الامتصاص الذري في أمصال ٢٠ امرأة من المصابات بمختلف السرطانات الأنثوية التناسلية و ١٥ امرأة من المصابات بالأورام التناسلية الحميدة. لوحظت زيادة معنوية ( $p < 0.05$ ) في مستوى النحاس لدى المصابات بالأورام السرطانية عند مقارنتها مع المصابات بالأورام الحميدة. أما عند تقدير مستوى الزنك فوجد انه ليس هناك اختلاف معنوي يذكر بين مستواه عند المصابات بالأورام السرطانية و المصابات بالأورام الحميدة. دل تقدير المحتوى النسيجي للنحاس والزنك على زيادة معنوية ( $p < 0.005$ ) للنحاس وانخفاض غير معنوي ( $p > 0.005$ ) للخارصين في الأنسجة الخبيثة نسبة إلى محتوياتها في الحميدة. بالإضافة الى ذلك كانت هناك علاقة وثيقة بين مستويات النحاس والزنك في المصل ومستوياتهم في النسيج بالأورام السرطانية، لكن لا توجد مثل هذه العلاقة في أمصال وأنسجة المصابات بالأورام الحميدة.

### Introduction

The blood serum levels of copper and zinc in malignant diseases have been the subject of a multitude of investigation and their possible involvement has been recognized in many cancerous conditions. High serum copper levels were found in divers hematological and lymphatic malignancies such as leukemia<sup>(1,2)</sup>. Hodgkin's diseases and malignant lymphoma<sup>(2,4,5)</sup>. Elevated serum copper and decreased serum zinc levels have been detected in patients with sarcoma<sup>(6,7)</sup> lung cancer<sup>(8,9)</sup> and carcinoma of digestive system<sup>(9,10)</sup>. Thus the serum copper and serum zinc

level ratio was found to be of great value in prognosis and therapy in these patients<sup>(6,10)</sup>. Free radicals in general and superoxide radical ion in particular have already been incriminated as the possible cause for cancer<sup>(11,12)</sup>. So this controversy on the concentrations of trace metals in serum and tissues has prompted us to investigate whether there were also such changes in gynecological cancer whether their was a relationship in serum and cancerous tissue obtained from the Patients with the gynecological cancer.

## Objectives

- 1-Predication of alterations in copper and zinc levels in serum and tissues of gynecologic tumor patients
- 2-Detecton of the relationship between copper and zinc levels in serum and their levels in tissue in cancer patients and patients with benign tumors

## Patients and methods

Twenty patients with gynecologic cancer were selected for the study .For the comparison of the result 30 normal control subjects who had been operated for benign diseases such as myoma were also included these tissue samples were immediately placed in a 5% formaldehyde solution until tested for copper and zinc .Fasting blood samples were draw into polyethylene tubes . Sera were separated and all samples stored at -70°C.All instruments used in this study were specially cleaned to avoid trace element contamination .One gram of tissue sample was immersed in a solution containing 2.5ml HNO<sub>3</sub> and 0.5 ml HClO<sub>4</sub>

for an hour. Then it was digested on a heat block at first 10°C and then 20°C.After digestion the solution was mixed with 1% v/v HNO<sub>3</sub>. The cu and zn concentration of this tissue solution and serum were determined by Perkin Elmer atomic absorption spectrophotometer calibration curves were determined using copper and zinc dissolved in HNO<sub>3</sub>/HClO<sub>4</sub>.The students t test was used for statistical evaluation of the data.

## Results and discussion

Serum and tissue levels of copper and zinc were measured in 20 gynecologic patients (5 ovary,9 uterus, 6 cervical ) and 15 benign tumor patients (pathological controls) .The results were analyzed using students t test it was found there were significant (p<0.05) elevations of serum copper and non significant (p>0.05)decreased of serum zinc in the cancer patients when compared with the pathological controls (table 1).

Table 1. Levels of copper and zinc in serum of gynecologic tumor patients and pathological controls

metal	Range	Mean ± SD	P value
Cu µg / ml			
pathological controls	0.88-1.25	1.04±3.2	P<0.05
Gynecologic cancer patient	0.98-2.05	1.64±1.15	
Zn µg /dl			
pathological controls	13.5-29.31	22.0±1.51	N.S P>0.05
Gynecologic cancer patients	12.2-26.5	20.7±1.2	

On the other hand, the results of evaluation of copper and zinc concentrations in tissues revealed significantly elevated (p<0.005)of copper and non significant

(p>0.05) decreased of zinc in malignant tissues when compared with those of benign tissues (table 2).

Table 2. Levels of copper and zinc in tissue of gynecologic tumor patients and pathological controls

metal	Range	Mean ± SD	P value
Cu µg / g			
pathological controls	0.8-2.5	1.48±0.81	P<0.005
Gynecologic cancer patients	1.35-2.88	2.1±0.52	
Zn µg /g			
pathological controls	10.2-28.8	18.8±2.31	N.S P>0.005
Gynecologic cancer patients	11.5-32	19.2±3.3	

The correlation of serum and tissue (benign and malignant) copper and zinc metals were examined statistically using the linear regression analysis (table 3) show the contents of two metals were correlated in sera and malignant tissue of gynecologic cancer patients copper and zinc were

observed to be positively correlated ( $r=0.93$  and  $p<0.0005$ ,  $r=0.86$  and  $p<0.005$ ) respectively no such correlation were indicated in sera and tissues of patients with benign disease.

Table 3. Results of unvaried analysis of copper and zinc contents in sera and tissues of gynecologic tumor patients

Subject	Benign tissue		Malignant tissue	
	r	P value	R	P value
Copper	0.4	N.S	0.93	P<0.0005
zinc	0.35	N.S	0.86	P<0.005

The real origin of the increased copper concentration in serum or tissue of various cancers seems to be unclear, and several possible explanation are considered; the exact mechanism of trace metals in concentration according to samuni et, al.<sup>(13)</sup>. Superoxide radicals or other reducing agents, such as ascorbate, reduce the copper complexes to the cuprous state .In turn, these complexes react with hydrogen peroxidesase to form hydroxyl radicals that damage proteins, RNA, and most importantly DNA.Repetitive formation of OH radicals at a specific location is probably the mechanism of this process. such a cause of events is an acceptable theory for explaining the involvement of copper in the malignancy it is of interest to note that serum and tissue of copper levels in gynecologic cancer were elevated when compared with the benign group. Some

workers reported elevated serum copper levels in cervical carcinoma<sup>(14, 15)</sup>, and in breast cancer<sup>(16)</sup>. The high copper tissue concentration has been investigated in various cancers including Hodgkin's disease and in malignant mesenchymoma, as well as the elevated copper laves in carcinomas of the large bowel, stomach<sup>(7, 13, 15)</sup>. Altintas et.al<sup>(17)</sup> have stated that tissue copper content showed non significant difference between early and advanced clinical stage of cervical carcinoma. In the present study we found significant elevation in tissue and serum copper in malignant compared with benign tumors, we believed that such elevation indicates the roles of copper in carcinogenesis tissues.

Serum zinc concentration have been reported to be decreased<sup>(13,14)</sup>. The behavior of the trace metal was tested by us both in benign and malignant tissues .The mean zinc

concentration in 20 malignant specimens did not statistically differ from 15 non malignant tissue samples (non significant increase in malignant tissues). Several studies have reported rises in zinc concentration while other have reported lower in zinc concentration for example the zinc concentration was significantly increased in malignant breast tissue as compared to its normal counterpart<sup>(18,15)</sup>. Whereas Daniesen et.al<sup>(19)</sup> have stated that tissue zinc content showed vastly lowered in hypernephromatic tissue and in kidney tissue was significantly decreased in the malignant tissue of this organ . These data unequivocally show that the alterations occurring in the zinc concentration of cancerous tissues follow a different pattern in each particular organ. This fact substantiates fursts<sup>(21)</sup> speculation that metals can be carcinogenic if their local cellular concentration becomes high so that they can compete with the normal essential metals for the available binding site in the lattice ,and thus aid in the synthesis of abnormal polymeric nucleic acids .Thus cancers for each tissue concentrates different metals ,Karicioglu et,al<sup>(22)</sup> assume that during the neoplastic growth of renal carcinoma the tubule cells lose their anatomical access to the glomerular filtrated consequently prohibit the intake of zinc by renal absorption.

The general trend towards slightly decreased zinc concentrations in malignant tissue ,as demonstrated in the current study supports the experimental results obtained by Brown et,al<sup>(23)</sup>. They suggest that zinc deficiencies associated with the etiology of cancer.

Several authors have found elevated copper levels in sera but not in tissue of patients with various cancer<sup>(12,18)</sup>. Sonmez et,al<sup>(24)</sup> have found an increase in levels of serum copper concentration that associated with marked elevation in tissue and serum sialyltransferase activities of breast cancer patients .The elevations was correlated with the grade (I ,II ,III ) of the disease .Fisher et,al<sup>(6)</sup> have showed that copper levels were elevated in cancerous tissue of sarcoma when compared with the normal tissue. Seuret et. al.<sup>(25)</sup> have demonstrated that the elevation of serum copper and decrease of zinc levels was comparable with the burden the tumor ,while tissue copper content showed no significant differences between early advanced clinical stage of the patient with endometrial neoplasia. Inustuka et,al<sup>(10)</sup> have reported rises in copper while the zinc level was low in both sera and tissues of patients with colon and stomach cancer . Our results are in agreement with those results .

Copper levels was found to be positively correlated in sera and malignant tissues .This observation may be explained by the fact that ceruloplasmin is resialylated at the tumor cell surface and the decrease in catabolism, which is due to this process ,could account for the increase in serum and tissue copper levels in patients with neoplasia<sup>(26)</sup>. However ,it has been proposed that copper level rise in sera of cancerous patients may be directed by the enhancement of tissue sialyltransferase activity . An enzyme has been observed to be elevated in sera and tissues of patients with different cancers<sup>(24, 26)</sup>.

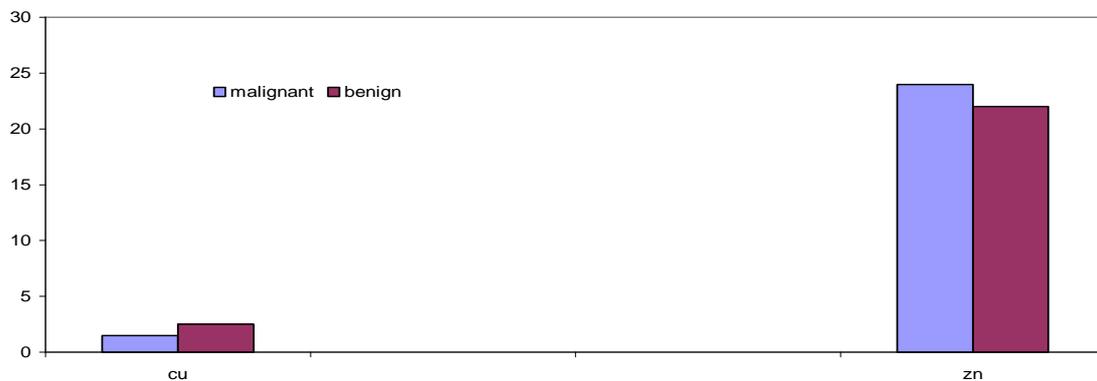


Fig (1): Mean of copper and zinc levels in serum of malignant and benign gynecologic tumors



Fig (2): Mean of copper and zinc in tissue of malignant and benign gynecologic tumors.

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