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Original Research Article

Association of serum copper, zinc level in invasive cervical cancer in a tertiary hospital

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ABSTRACT

Background: Cervical cancer remains a significant global health concern. The present study was conducted to assess the relationship between serum copper and zinc levels in individuals diagnosed with cervical cancer. The aim of this study was to assess the association between serum copper and zinc levels in invasive cervical cancer in a tertiary hospital.
Methods: This case-control study was conducted among 122 women, aged 25-65, attending the outpatient department and Colposcopy Clinic of the Department of Gynecological Oncology, BSMMU, Dhaka, from April 2022 to March 2023. The cases (n=61) had histopathologically confirmed cervical cancer, while the controls (n=61) had normal cervixes. Serum copper and zinc levels were measured at the Laboratory of Biochemistry and Molecular Biology, BSMMU. Data were analyzed using Microsoft Excel and SPSS v27.0.
Results: The study revealed that cervical cancer cases had significantly higher serum copper levels and a 6.4 times higher risk when copper levels were ≥140.0 mcg/dl. Serum zinc levels were significantly lower in cases, with a 3.9 times higher risk when zinc levels were <68 mcg/dl. Additionally, the Cu/Zn ratio was higher in cases, and a ratio >1.87 conferred a 4.5 times higher risk of cervical carcinoma.
Conclusions: Elevated copper, reduced zinc, and a higher copper-zinc ratio were observed in cervical cancer patients, suggesting a potential association with cervical cancer risk and warranting further investigation for clinical applications in early detection and management.

Keywords: Cervical cancer, Copper, Cu/Zn ratio, Serum trace elements, Zinc

INTRODUCTION

Cervical cancer, a malignant condition that originates in the cells of the cervix or the cervical neck area, is a significant global health concern.[1] The impact of this disease on women's lives is profound, leading to premature mortality and prolonged disability. Consequently, there is a significant opportunity to reduce both the incidence and mortality associated with this disease through early detection and timely medical intervention.[2]

Cervical cancer is the fourth most common cancer in women worldwide, following breast, colon, and lung cancer. According to GLOBOCAN 2020 estimates, approximately 604,000 new cases of cervical cancer were registered annually, resulting in approximately 342,000

deaths. The South Asian region accounts for one-fourth of the global incidence of cervical cancer.[3]

Persistent infection, particularly with oncogenic types of human papillomavirus (HPV), marked by the ongoing presence of the same type-specific HPV DNA in multiple samples collected over a span of 6 to 12 months, is a substantial contributor to the development of cervical cancer.[4] While HPV infection serves as a necessary factor in cervical cancer development, additional associated co-factors play a crucial role. These co-factors may include long-term use of oral contraceptive pills (OCPs), co-infection with the human immunodeficiency virus (HIV), high parity, presence of herpes simplex virus (HSV) infection, chlamydia trachomatis (CT) infection, lack of male circumcision, compromised immune function, and nutritional and dietary factors.[5]

In 2020, the World Health Organization (WHO) introduced a global strategy aimed at eliminating cervical cancer as a public health threat by 2030. As cervical cancer is a preventable disease, it is important to identify the co-factors associated with it.[6] Trace elements play a crucial role in biological processes, acting as cofactors for antioxidant enzymes and influencing cell proliferation and differentiation. Disturbances in trace element levels can have deleterious effects on human health and disrupt the delicate balance between free radical formation and antioxidant defense in a healthy system.[7,8] Exposure to reactive oxygen radicals can cause DNA damage, mutation, and carcinogenesis based on altered trace element levels.[7]

Cancerous cells may consume circulating zinc for tumor growth and membrane stability, potentially leading to lower zinc levels in cancer patients.[9] Zinc also exerts an anticarcinogenic effect in processes such as DNA synthesis, RNA transcription, immune functions, cell division, and growth.[10] It acts as a free-radical scavenger or antioxidant, and its deficiency may contribute to the initiation and progression of cervical cancer.[11]

Copper ions can enhance the formation of harmful free radicals. Copper is essential for the proper functioning of various metalloenzymes and has been found to be elevated in the serum of various cancer types.[12] The serum Cu/Zn ratio is a major determinant in detecting malignant gynecological tumors.[11]

Some studies have indicated that cervical cancer patients tend to have higher serum copper levels and lower zinc levels compared to controls.[13,14] The present study was conducted to assess the relationship between serum copper and zinc levels in individuals diagnosed with cervical cancer. In the context of Bangladesh, this study's findings could have important implications for understanding the role of serum copper and zinc levels in cervical cancer risk and potentially guide preventive measures and therapeutic purposes. The aim of this study was to assess the association between serum copper and zinc levels in invasive cervical cancer in a tertiary hospital.

METHODS

This case-control study was conducted at the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka, over a 12-month period from April 2022 to March 2023. The study population comprised 122 women aged 25 to 65 years attending the outpatient department and Colposcopy Clinic of the Department of Gynecological Oncology at BSMMU, including 61 cases and 61 controls. Cases were selected based on their histopathological findings of cervical cancer, and controls were histopathology-proven normal women.

Inclusion criteria

Case: Women aged 25-65 years with histopathology-confirmed cervical cancer who provided consent to participate in the study were included.

Control: Age-matched women with histopathology-confirmed normal cervix who provided consent to participate in the study were included.

Exclusion criteria

Pregnant women, women with cervical intra-epithelial neoplasia, women with chronic renal disease and chronic liver disease, women with malignancies other than cervical cancer, women who were treated for cervical cancer, and women who were taking zinc or any trace element supplementation in the past three months were excluded.

Institutional approval and ethical clearance were obtained from the IRB of BSMMU, and informed written consent was secured from all participants. Data collection included face-to-face interviews to gather demographic and clinical information. Participants attended the colposcopy clinic and outpatient department, where biopsies were taken from women with visible cervical growths and from VIA-positive cases. The histopathological analysis confirmed the diagnosis of invasive cervical cancer in the cases and established the normalcy of the controls. Detailed histories and physical examinations were conducted, and blood samples were analyzed for serum zinc and copper levels using a Thermo Scientific™ Indiko™ Plus Clinical Chemistry Analyzer. Anthropometric measurements were taken to calculate BMI. Statistical analyses were performed using SPSS version 27.0, with significance set at $p<0.05$.

RESULTS

Table 1 shows the distribution of socio-demographic characteristics between the case (women with cervical carcinoma) and control (women with normal cervix) groups. The characteristics include age, occupation, and

social status according to monthly family income. No significant differences were observed in these characteristics between the two groups (p>0.05 for all comparisons).

Table 1: Distribution of the respondents according to socio-demographic characteristics by group (case=61, control=61).

Socio-demographic variables		Case		Control		P value
		Number (n=61)	Percentage	Number (n=61)	Percentage	
Age (in years)	25-39	31	61.80	32	52.50	0.074[a]
	40-54	21	34.40	27	44.30	
	≥55	9	14.80	2	3.30	
	Mean ± SD	40.84±10.44		38.67±8.18		0.205[b]
Occupation	Housewife	55	90.20	47	77.00	0.127[c]
	Service holder	5	8.20	12	19.70	
	Day laborer	1	1.60	2	3.30	
Social status according to monthly family income (in BDT)	Lower class (≤7,378 Tk.)	28	45.90	19	31.10	0.273[c]
	Lower middle class (7,379-28,810 Tk.)	23	37.70	30	49.20	
	Upper middle class (28,811-89,280 Tk.)	10	16.40	11	18.00	
	Upper class (≥89,281 Tk.)	0	0.00	1	1.60	

[a]Chi square test was done to measure the level of significance; [b]Unpaired-t test was done to measure the level of significance; [c]Fisher's exact test was done to measure the level of significance.

Table 2: Distribution of mean (±SD) copper and zinc levels, and copper-zinc ratio by group (case=61, control=61).

Parameters		Case	Control	P value
		Number (N=61)	Number (N=61)	
Serum copper level (mcg/dl)	Mean±SD	132.92±64.39	110.34±53.67	0.037[b]
Serum zinc level (mcg/dl)	Mean±SD	63.29±36.39	80.65±23.01	0.002[b]
Cu/Zn ratio	Mean±SD	3.35±3.01	1.43±0.63	<0.001[b]

[b]Unpaired-t test was done to measure the level of significance.

Table 3: Odds ratios (OR) and 95% confidence intervals (CI) for cervical carcinoma according to serum copper levels, zinc levels, and copper-zinc ratio (case=61, control=61).

Variables		Case (N=61)	Control (N=61)	P value	Odd's Ratio	95% CI (lower-upper)
Serum copper level (mcg/dl)	≥140.0 mcg/dl	32 (52.5)	9 (14.8)	<0.001[a]	6.375	2.677-15.185
	<140 mcg/dl	29 (47.5)	52 (85.2)			
Serum zinc level (mcg/dl)	<68 mcg/dl	37 (60.7)	17 (27.9)	<0.001[a]	3.990	1.867-8.530
	≥68 mcg/dl	24 (39.3)	44 (72.1)			
Cu/Zn ratio	>1.87	32 (52.5)	12 (19.7)	<0.001[a]	4.506	2.011-10.097
	≤1.87	29 (47.5)	49 (80.3)			

[a]Chi square test was done to measure the level of significance.

Serum copper levels were significantly higher in the case group (132.92±64.39 mcg/dl) compared to the control group (110.34±53.67 mcg/dl), with a p-value of 0.037. Conversely, serum zinc levels were significantly lower in the case group (63.29±36.39 mcg/dl) compared to the control group (80.65±23.01 mcg/dl), with a p value of 0.002.

Additionally, the Cu/Zn ratio was notably elevated in the cervical cancer patients of the case group compared to the healthy women in the control group, with values of 3.35±3.01 and 1.43±0.63, respectively. This difference was statistically highly significant (p<0.001) (Table 2).

Respondents with serum copper levels of ≥140.0 mcg/dl had a significantly increased risk of cervical carcinoma, with an odds ratio of 6.375 (95% CI = 2.677-15.185) compared to those with copper levels <140 mcg/dl (p<0.001). Similarly, those with serum zinc levels <68 mcg/dL had a 3.990-fold increased risk of cervical

carcinoma compared to women with zinc levels ≥68 mcg/dl (95% CI = 1.867-8.530; p<0.001). Additionally, a higher copper to zinc ratio (>1.87) was associated with a 4.506 times greater likelihood of cervical carcinoma compared to a ratio ≤1.87 (95% CI = 2.011-10.097; p<0.001) (Table 3).

DISCUSSION

Cervical cancer is a largely preventable disease and also highly treatable if detected and treated early. Even in advanced stages, the disease can be effectively controlled with appropriate treatment and palliative care. Zinc and copper are essential trace elements in the human diet and play a crucial role in various physiological processes. The aim of this study was to explore the possible association between zinc deficiency, elevated serum copper levels, and cervical cancer and to provide insights that could serve as the basis for preventive and therapeutic strategies for this widespread and serious health problem.

In this case-control study, a total of 122 women were purposively included. Sixty-one histopathology-confirmed cervical cancer women were enrolled in the case group, and the remaining 61 women with histologically normal cervix were included in the control group. Both groups were compared for their socio-demographic, and risk-related factors, as well as serum zinc and copper levels.

In the present study, the majority of the respondents were 25-39 years old (cases: 61.8% vs. controls: 52.5%; p=0.074), and the mean age among the cases was slightly higher (40.84±10.44 years) than the control group women (38.67±8.18 years), with a p value of 0.205. Most of the participants' occupation was housewife (cases: 90.2% vs. controls: 77.0%; p value = 0.127). The majority of the respondents belonged to lower middle-class social status (cases: 37.7% vs. controls: 49.2%; p=0.273). Similar findings were observed in an Indian study by Thovarayi et al, who noted that the study population had a mean age of 43.17±13.43 years, ranging from 21 to 65 years.[15] A significant portion had a high school education (151, 37.1%), while the majority had a monthly income below 5000 rupees (207, 40%).

In the current study, it was observed that the serum copper level was significantly higher among the cases compared to the controls (132.92±64.39 vs. 110.34±53.67 mcg/dl; p=0.037). Moreover, the odds ratio calculation demonstrated a 6.4 times higher risk of developing cervical cancer in patients with a serum copper level of ≥140.0 mcg/dl, as opposed to women with a copper level of <140 mcg/dl (p<0.001; OR=6.375; 95% CI=2.677-15.185).

The mean serum zinc level among the cases was significantly lower compared to that of the controls (63.29±36.39 vs. 80.65±23.01 mcg/dl; p=0.002). The odds ratio calculation demonstrated a 3.9 times higher risk of developing cervical cancer in patients with a serum zinc level of <68 mcg/dl compared to the women with serum zinc levels ≥68 mcg/dl (OR=3.990; 95% CI=1.867-8.530; p<0.001).

The mean Cu/Zn ratio was also found to be higher among the case group of women (3.35±3.01) compared to the control group (1.43±0.63) of respondents (p<0.001). The respondents with a copper to zinc ratio >1.87 had a 4.5 times higher chance of having cervical carcinoma compared to the women with a Cu/Zn ratio ≤1.87 (p<0.001; OR=4.506; 95% CI=2.011-10.097). Several previous studies also documented similar findings.

Okunade et al revealed that the mean serum level of zinc was significantly lower in the cervical cancer group than in the cancer-free control group (70.1±11.7 µg/dl vs. 105.8±16.5 µg/dl; p=0.003).[16] MeGhana et al found that plasma copper levels were 118±49.9 µg/dl in cases and 100±23.2 µg/dl in controls (p=0.25), while plasma zinc levels were 58.4±11.7 µg/dl in cases and 65.4±31.9 µg/dl in controls (p=0.46).[17] The Cu/Zn ratio was 2.1±1.08 µg/dl in cases and 1.8±0.88 µg/dl in controls (p=0.42).

Cunzhi et al showed that serum Cu level and Cu/Zn ratio were significantly higher in the cervical cancer group than the uterine myoma group (p<0.01).[13] In a pilot study, Tiwari et al.[18] found a significant difference in the mean values of serum Zn between group 1 with a complete response in locally advanced cancer cervix patients receiving chemo-irradiation and group 2 with partial/no response (p=0.0463). The standard error of difference was 0.009 at a 95% confidence interval. Xie et al conducted a meta-analysis, revealing significantly lower serum zinc levels in cervical cancer cases compared to controls (summary SMD -1.379, 95% CI -1.527, -1.231), especially among Asian populations (summary SMD -1.391, 95% CI -1.543, -1.239), albeit with high heterogeneity (I2=98.8%).[19]

Ma et al in their study of a mixed-ligand copper (II) complex that inhibits growth and induces apoptosis by DNA targeting in human epithelial cervical cancer cells, suggested that the complex was capable of promoting HeLa cell apoptosis through an oxidative DNA damage pathway.[20]

Based on these findings, it is evident that patients with invasive cervical carcinoma exhibit elevated serum copper levels and copper-zinc ratios, while there is a significant decrease in serum zinc levels among cervical cancer patients.

This study had several limitations. It was conducted in a single tertiary-level hospital, which may limit the diversity of the sample. The sample was not randomly selected, potentially introducing selection bias. The sample size was relatively small, affecting the statistical power of the findings. The relationship between copper and zinc levels and different stages of cervical cancer was not assessed.

Consequently, the findings of this study cannot be generalized to the entire population.

CONCLUSION

The study findings indicate that patients with cervical cancer generally exhibit elevated serum copper levels and reduced serum zinc levels compared to women with a healthy cervix. Additionally, a higher serum copper-to-zinc ratio is associated with cervical cancer, suggesting a potential biomarker for the disease.

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