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Research Article

Relationship Between Serum Copper, Zinc Level and Tumour Aggressiveness in Invasive Cervical Cancer

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Abstract

Background: Cervical cancer, a leading cause of cancer-related morbidity and mortality, exhibits considerable variability in aggressiveness. The role of trace elements such as copper and zinc in influencing tumor behavior and progression has garnered attention. This study investigates the relationship between serum copper and zinc levels and tumor aggressiveness in invasive cervical cancer. *Methods:* A cross-sectional comparative study was conducted among 150 women with invasive cervical cancer attending the outpatient department and Colposcopy Clinic of the Department of Gynecological Oncology, BSMMU, Dhaka, from April 2022 to March 2023. Participants were divided into two groups based on tumor aggressiveness: Group 1 (less aggressive) and Group 2 (more aggressive), with 75 women in each group. Serum copper and zinc levels were measured and analyzed for differences between groups. *Result:* Serum copper levels were significantly higher in Group 2 (152.31 ± 41.81 µg/dL) compared to Group 1 (139.31 ± 25.52 µg/dL) with a p-value of 0.023. Conversely, serum zinc levels were significantly lower in Group 2 (55.24 ± 28.13 µg/dL) compared to Group 1 (66.29 ± 31.58 µg/dL) with a p-value of 0.025. The copper/zinc ratio was significantly higher in Group 2 (2.76 ± 1.20) compared to Group 1 (2.10 ± 1.00) with a p-value of <0.001. *Conclusion:* Elevated serum copper levels and copper/zinc ratio, along with decreased zinc levels, are associated with more aggressive cervical cancer. These findings suggest that trace element imbalances may serve as biomarkers for assessing tumor aggressiveness and could inform future therapeutic strategies.

Keywords

Cervical Cancer, Copper, Zinc, Tumor Aggressiveness, Biomarker

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1. Introduction

Cervical cancer represents a significant global health challenge, characterized by substantial morbidity and mortality rates [1]. It is particularly prevalent in developing countries, where limited access to healthcare resources, including screening and preventive measures, exacerbates the burden of the disease [2]. The progression of invasive cervical cancer varies widely, presenting as either indolent tumors that grow slowly or highly aggressive forms that proliferate rapidly and metastasize early [3]. This variability in tumor behavior poses considerable difficulties in treatment planning and affects patient prognosis, underscoring the need for a deeper understanding of the factors influencing tumor aggressiveness [4].

Invasive cervical cancer typically arises from persistent infection with high-risk human papillomavirus (HPV) types, leading to dysplastic changes in cervical epithelial cells [5]. Over time, these changes can progress to invasive cancer if left untreated [6]. The disease progression is influenced by numerous factors, including genetic, environmental, and biochemical components [6]. Despite advances in screening and vaccination, cervical cancer remains a leading cause of cancer-related deaths in women, highlighting the urgent need for improved diagnostic and therapeutic strategies [7].

Recent research has increasingly spotlighted the role of trace elements, particularly copper and zinc, in cancer biology [8]. These elements, while essential for various physiological processes, have been shown to impact tumor characteristics and progression in complex ways [9]. Their roles in cancer are multifaceted, involving mechanisms related to cellular growth, immune response, and oxidative stress.

Copper is an essential trace element that serves as a cofactor for several enzymes involved in critical physiological processes. It plays a significant role in angiogenesis, which is the formation of new blood vessels, a process crucial for tumor growth and metastasis. Elevated copper levels have been observed in various malignancies, including cervical cancer [10]. The link between copper and cancer aggressiveness is thought to be related to copper's role in promoting angiogenic processes. Enzymes such as lysyl oxidase, which require copper as a cofactor, are involved in the cross-linking of collagen and elastin in the extracellular matrix [11]. This modification enhances the structural integrity of tissues and facilitates tumor invasion and metastasis. Therefore, elevated copper levels might contribute to a more aggressive tumor phenotype by supporting these processes.

Moreover, copper has been implicated in the regulation of oxidative stress and cellular proliferation. Increased copper levels can exacerbate oxidative stress by promoting the production of reactive oxygen species (ROS), which in turn can lead to DNA damage and cancer progression [12]. The association between high copper levels and poor prognosis in cancer patients has been noted in several studies, suggesting that copper could serve as a biomarker for tumor aggressiveness and treatment response.

In contrast, zinc is known for its protective effects against cancer development. It is an essential component of various enzymes involved in DNA repair, cell division, and immune function. Zinc deficiency has been linked to impaired immune responses, increased oxidative stress, and enhanced cancer susceptibility [13]. The role of zinc in maintaining cellular stability and function makes it a critical factor in cancer biology. Lower zinc levels have been associated with more aggressive forms of cancer, including cervical cancer [14]. Zinc deficiency can impair the body's ability to regulate apoptosis (programmed cell death) and repair DNA, potentially leading to increased tumor progression and poorer clinical outcomes.

The balance between copper and zinc is crucial, as both elements interact in various biochemical pathways. An imbalance, characterized by elevated copper levels and decreased zinc levels, has been observed in some cancers and may contribute to tumor progression [15]. This imbalance can affect the body's ability to manage oxidative stress and maintain cellular homeostasis, further influencing cancer aggressiveness.

2. Objective

The primary objective of this study is to assess the relationship between serum copper and zinc levels and the aggressiveness of invasive cervical cancer.

3. Methodology & Materials

This cross-sectional comparative study was conducted at the outpatient department and Colposcopy Clinic of the Department of Gynecological Oncology, BSMMU, Dhaka, from April 2022 to March 2023. A total of 150 women aged 25 to 65 years, diagnosed with invasive cervical cancer, were purposively selected and divided into two groups based on the aggressiveness of their tumors. Group 1 consisted of 75 women with less aggressive tumors, characterized by early-stage (I-IIa) cancer and lower histopathological grade (G-1 and G-2). Group 2 included 75 women with more aggressive tumors, identified by advanced-stage (IIb-IV) cancer and higher histopathological grade (G-3). Clinical data, including demographic information, medical history, and cancer staging, were recorded. Tumor aggressiveness was assessed through clinical staging and histopathological examination. Blood samples were collected from all participants, and serum copper and zinc levels were measured using atomic absorption spectrophotometry. Data were analyzed using SPSS (version 27.0), with continuous variables expressed as mean ± standard deviation and compared between groups using the independent samples t-test. Categorical variables were compared using the Chi-square test or Fisher's exact test, with a p-value of <0.05 considered statistically significant. Ethical

approval was obtained from the Institutional Review Board (IRB) of BSMMU, and informed consent was secured from all participants. The study adhered to the principles outlined in the Declaration of Helsinki, ensuring confidentiality and ethical treatment of participants.

4. Result

Table 1. *Demographic Characteristics of Study Participants (N = 150).*

Characteristics		Group 1 (n=75)	Group 2 (n=75)	p-value
Age (years)		48.2 ± 8.3	49.1 ± 7.9	0.402
Parity	0 - 2	12 (16%)	14 (19%)	0.663
	≥ 3	63 (84%)	61 (81%)	
Socioeconomic Status	Low	51 (68%)	48 (64%)	0.605
	Middle/High	24 (32%)	27 (36%)	

Table 1 summarizes the demographic characteristics of 150 participants, with 75 women in each group. The mean age was similar between Group 1 (48.2 ± 8.3 years) and Group 2 (49.1 ± 7.9 years), with no significant difference (p=0.402). Parity was also comparable, with 16% Low parity in Group 1 and 19% in Group 2, while the majority were multiparous (84% and 81%, respectively; p=0.663). Most participants in both groups had low socioeconomic status (68% in Group 1 and 64% in Group 2; p=0.605) respectively.

Table 2. *Serum Copper and Zinc Levels in Study Participants (N = 150).*

Parameter	Group 1 (n=75)	Group 2 (n=75)	p-value
Serum Copper (µg/dL)	139.31 ± 25.52	152.31 ± 41.81	0.023
Serum Zinc (µg/dL)	66.29 ± 31.58	55.24 ± 28.13	0.025

Table 2 presents the serum copper and zinc levels among the study participants, divided into two groups based on tumor aggressiveness. Group 1, comprising 75 participants with less aggressive tumors, had an average serum copper level of 139.31 ± 25.52 µg/dL and an average serum zinc level of 66.29 ± 31.58 µg/dL. In contrast, Group 2, which included 75 participants with more aggressive tumors, showed significantly higher serum copper levels (152.31 ± 41.81 µg/dL) and lower serum zinc levels (55.24 ± 28.13 µg/dL). The differences between the two groups were statistically significant, with p-values of 0.023 for serum copper and 0.025 for serum zinc.

Table 3 compares the serum copper/zinc ratio between the two groups of study participants. Group 1, which includes 75 participants with less aggressive tumors, had a mean copper/zinc ratio of 2.10 ± 1.00. In contrast, Group 2, consisting of 75 participants with more aggressive tumors, had a significantly higher mean copper/zinc ratio of 2.76 ± 1.20. The difference between the two groups is statistically significant, with a p-value of less than 0.001. This suggests that a higher copper/zinc ratio may be associated with increased tumor aggressiveness in invasive cervical cancer.

Table 3. *Comparison of Serum Copper/Zinc Ratio between Groups (N = 150).*

Ratio	Group 1 (n=75)	Group 2 (n=75)	p-value
Copper/Zinc Ratio	2.10 ± 1.00	2.76 ± 1.20	< 0.001

5. Discussion

This study aimed to investigate the relationship between serum copper and zinc levels, as well as their ratio, with tumor aggressiveness in patients with invasive cervical cancer. The

findings suggest a significant association between higher serum copper levels, lower serum zinc levels, and an elevated copper/zinc ratio with increased tumor aggressiveness. These results align with existing literature, highlighting the potential role of trace elements in the pathophysiology of cervical cancer.

Copper is an essential trace element involved in various biological processes, including angiogenesis, immune function, and oxidative stress. Previous studies have reported elevated serum copper levels in various cancers, including cervical cancer. For instance, a study by Yucel et al., found that serum copper levels were significantly higher in patients with cervical cancer compared to healthy controls, with mean levels of 133.6 ±28.9 μg/dL in the cancer group versus 95.4 ± 17.2 μg/dL in the control group [16]. Similarly, our study observed higher copper levels in patients with more aggressive tumors (152.31 ± 41.81 μg/dL) compared to those with less aggressive tumors (139.31 ± 25.52 μg/dL), further supporting the hypothesis that elevated copper levels may contribute to cancer progression.

Zinc, on the other hand, is a critical component of numerous enzymes and proteins, playing a vital role in DNA repair, apoptosis, and immune response. In contrast to copper, zinc levels are often found to be decreased in cancer patients. A study by Varghese et al., reported significantly lower serum zinc levels in cervical cancer patients compared to healthy controls, with mean levels of 69.4 ±12.3 μg/dL in the cancer group and 84.7 ± 10.8 μg/dL in the control group [17]. Our findings are consistent with this observation, as we found lower zinc levels in patients with more aggressive tumors (55.24 ±28.13 μg/dL) compared to those with less aggressive tumors (66.29 ± 31.58 μg/dL). The reduction in zinc levels could be attributed to the increased demand for zinc in rapidly proliferating tumor cells, leading to its depletion in the serum.

The copper/zinc ratio is an important marker that has been studied in various malignancies. A higher copper/zinc ratio has been associated with poor prognosis in several cancers, including cervical cancer. Kanthasamy et al., demonstrated that a higher copper/zinc ratio was correlated with advanced disease stages and lower survival rates in cervical cancer patients, with a mean ratio of 3.01 ± 1.2 in advanced stages compared to 2.19 ± 0.9 in early stages [18]. Our study corroborates these findings, showing a significantly higher copper/zinc ratio in patients with more aggressive tumors (2.76 ± 1.20) compared to those with less aggressive tumors (2.10 ± 1.00). The elevated copper/zinc ratio could reflect an imbalance in the oxidative stress response, where increased copper levels promote oxidative damage while decreased zinc levels impair antioxidant defense mechanisms.

Several mechanisms have been proposed to explain the role of copper and zinc in cancer progression. Copper is a cofactor for several enzymes involved in angiogenesis, such as ceruloplasmin and cytochrome c oxidase. Increased copper levels may enhance tumor angiogenesis, providing the necessary blood supply for tumor growth and metastasis [19]. Additionally, copper is involved in the formation of reactive oxygen species (ROS), which can cause DNA damage and promote carcinogenesis [20]. On the other hand, zinc is known for its antioxidant properties and its role in DNA repair. A deficiency in zinc can lead to impaired DNA repair mechanisms, making cells more susceptible to genetic mutations and malignant transformation [21].

In contrast to our findings, some studies have reported no significant association between copper and zinc levels and cervical cancer aggressiveness. For example, Singh et al., conducted a study on Indian women with cervical cancer and found no significant difference in serum copper and zinc levels between early and advanced-stage patients [22]. The discrepancy between studies could be attributed to differences in study populations, sample sizes, and methodological approaches. However, the majority of studies, including ours, support the notion that an imbalance in copper and zinc homeostasis is linked to cancer progression.

Furthermore, a study by Liu et al., explored the role of the copper transporter ATP7B in cervical cancer. They found that ATP7B expression was significantly upregulated in cervical cancer tissues and was associated with increased serum copper levels and poor prognosis. Their findings suggest that targeting copper metabolism could be a potential therapeutic strategy for cervical cancer [23]. This is in line with our observation that higher serum copper levels are associated with more aggressive tumor behavior, indicating that copper could serve as a potential biomarker for cervical cancer prognosis.

The role of zinc in modulating immune responses is also noteworthy. Zinc deficiency has been shown to impair the function of natural killer (NK) cells and T-lymphocytes, which are crucial for anti-tumor immunity. A study by Prasad et al., reported that zinc supplementation improved the immune response in cervical cancer patients undergoing radiotherapy, leading to better treatment outcomes [24]. This underscores the importance of maintaining adequate zinc levels in cancer patients to support the immune system and potentially improve prognosis.

The clinical implications of our findings are significant. Monitoring serum copper and zinc levels, along with the copper/zinc ratio, could provide valuable insights into tumor aggressiveness in cervical cancer patients. These biomarkers could be used to identify patients at higher risk of disease progression and tailor treatment strategies accordingly. For instance, patients with a higher copper/zinc ratio might benefit from therapies targeting copper metabolism or antioxidant supplementation to counteract the effects of elevated copper levels and depleted zinc levels.

6. Limitations of the Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community. Including a control group would strengthen the

ability to discern whether observed changes in trace element levels are specifically associated with cancer aggressiveness. Future research would benefit from a longitudinal approach to monitor changes in serum copper and zinc levels over time, from diagnosis through treatment and follow-up, to better understand the causal relationships between these trace elements and tumor progression.

7. Conclusion

Our study's findings contribute to the understanding of how trace elements like copper and zinc influence cancer progression. Elevated serum copper levels and a higher copper/zinc ratio, along with lower zinc levels, are associated with more aggressive cervical tumors. These results support the hypothesis that trace element imbalances can impact tumor behavior and may serve as useful biomarkers for assessing cancer aggressiveness.

Abbreviations

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Author Contributions

Naznine Akter: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Syfun Naher: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization

Mahfuza Akhter: Funding acquisition, Project administration, Resources, Validation

Mahbuba Akhter Jahan: Conceptualization, Data curation, Formal Analysis, Methodology, Software, Visualization, Writing – review & editing

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Ethical Approval

The study Was approved by the Institutional Ethics Committee.

Conflicts of Interest

The authors declare no conflicts of interest.

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