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THE PLASMA CONCENTRATIONS OF ESSENTIAL TRACE ELEMENTS IN WOMEN WITH CANCER OF BREAST- OR CERVIX

M.A. Jimoh[1], B.O. Popoola[2], G.O. Arinola[3]

1. Department of Radiation Oncology, University of Ibadan, Nigeria.
2. Faculty of Allied Health Sciences, Baze University, Abuja
3. Department of Immunology, University of Ibadan, Nigeria.

Correspondence:
Prof. G.O. Arinola
Department of Immunology,
University of Ibadan,
Nigeria.
E-mail: drarinolaog64@yahoo.com.

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ABSTRACT

***Background*: Derangement of trace elements which could be due to systemic inflammation or oxidative stress is thought to be directly or indirectly involved in carcinogenesis.**

Aim is to evaluate plasma trace elements in female patients with cancer of breast- or cervix.

***Material and Methods*: This study was carried out in the Departments of Immunology and Radiation Oncology, University of Ibadan, Nigeria. Thirty (30) patients with cervical cancer, 30 patients with breast cancer and 30 age-matched females without cancer as control were included in the study. Plasma separated from venous blood was analysed for the concentrations of zinc (Zn), iron (Fe), selenium (Se) and copper (Cu) using Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES). The sixty cancer patients were newly diagnosed and in a stable state.**

***Results:* The mean plasma levels of Fe and Cu were significantly reduced in patients with breast cancer- or cervical cancer compared with control. The plasma concentrations of Fe, Cu, Zn and Se were significantly reduced in all patients having breast cancer and those in stage 2 compared with cervical cancer patients.**

***Conclusion*: Available data further support a previous suggestion that blood levels of metal varies with different cancers. Thus, a need for differential supplementation based on cancer types when modulation of trace element levels becomes a therapeutic option.**

Keywords: Cancers, Trace elements, Oxidative stress, Metal-binding-proteins, Therapeutic.

INTRODUCTION

Cancer is a complex disease characterised by unhindered multiplication and infiltration magnitude, which progresses from un-spread (Stage 1) to enlarged tumours entering into the adjacent tissues (as stage II or III) and other organs (Stage IV).[1] Each of these cancer stages or cancer type was reported to need personalised therapy or treatment intensity.[2] Besides genetic changes, tumour cells are denoted by sizeable changes in their metabolism influencing the demand for macronutrients and micronutrients.[3] This, thus account for the potential roles of trace elements as diagnostic or prognostic markers of cancers.[3] We aim to test the proposition of whether levels of the trace element selenium (Se), iron (Fe), copper (Cu) and zinc (Zn) are appropriate differentiators of two most prevalent female cancers (breast- and cervical- cancers).

Trace elements are involved in many biochemical processes supporting life. However, disruption of the balance between free radicals and antioxidants as a result of excesses or deficiencies of trace elements may cause a cellular and DNA injuries triggering carcinogenesis.[4] Selenium based proteins (selenoprotein P and plasma glutathione peroxidase), Cu-binding protein (caeruloplasmin), Zn-associated enzymes and Fe-transport proteins (ferritin and transferrin) are usually affected by conditions in cancer patients such as inflammation or hydration status.[5,6] These conditions are common to cancer patients. This therefore supports the basis for the present study. The involvement of Fe is not clear, though it differs with regard to tissue type and cancer progression. The changes in Fe concentrations were related to altered expression levels of Fe-regulatory proteins in breast cancer pathogenesis.[7] Of the approximately 115 elements known, only 19 are absolutely required in the human diet called essential elements. Therefore, an essential element is one that is required for life and whose absence results in death.[3,4]

An Indian study concluded that higher Cu serum level in breast cancer patients with respect to healthy

subjects.[8] Another study on serum Cu levels, found no significant difference between cancer patients and healthy females.[9] In contrast, another study reported increased serum Cu levels in patients with benign breast cancer[10]. Reduced serum Zn levels in most patients with breast cancer have been linked to an aberrant expression of Zn transporters.[11] Low serum levels of Zn or Se was found in cervical cancer patients but no difference was reportedin the serum level of Cu among cervical cancer patients compared to their cancer-free control.[12] In another study, low serum Zn, Se and Cu were reported in cervical cancer patients compared with healthy female control.[3,4] Variations in blood levels of trace elements was reported to be different based on differences in geographical location, gender, age, sample size, sample collection, tumour grade, cancer stages, cancer types, management strategy, race, analytical method, immune status and associated complications among other factors.[8-12] Based on above observations, the present study determined the plasma levels of Zn, Cu, Se and Fe in female Nigerians with breast- or cervical cancer. The strength of present study is the comparison of plasma trace elements in two female cancers.

MATERIALS AND METHODS

Following institutional ethical approval (UI/EC/23/0065), 5ml of blood was collected from newly diagnosed 30 patients with cervical cancer, 30 patients with breast cancer and 30 females without cancer as control subjects. Plasma separated from venous blood was analysed for the levels of Zn, Fe, Se and Cu by Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES). The mean and standard deviations of the data were presented as Tables and the difference between mean (± standard deviation) of the heavy metals between two groups was determined by Student *t*-test. $p \leq 0.05$ was taken as significant. All participants on any form of supplementation were excluded. Also, all participants were female Nigerians of the same ethnicity. They reported no bleeding, no weight loss, were actively mobile, not on previous compulsory medications, not smoking and not drinking alcohol. Also, they were married, self employed and with at least primary school education. All cancer patients were in stage 2 without metastasis.

RESULTS

Mean plasma concentrations of Fe and Cu were significantly decreased in patients with breast cancer- or cervical cancer compared with controls. However, the mean plasma concentration of Zn or Se was not significantly different in patients with breast cancer- or cervical cancer compared to control. But, mean plasma concentrations of Fe, Cu, Zn and Se were significantly decreased in patients having breast cancer compared to patients with cervical cancer. See Table 1. As presented in Table 2, the plasma concentrations of Fe, Cu, Zn and Se were significantly reduced breast cancer patients compared to cervical cancer- patients at stage 2.

Table 1: Concentrations (Mean±S.D) of essential trace metals in the plasma of female patients with breast- or cervical- cancer compared with healthy control

Variable	Breast Cancer (n=30)	Cervical Cancer (n=30)	Control (n=30)	t-, p-values Cca vs C	t-, p-values Bca vs C	t-, p-values Cca vs Bca
Fe (ug/dL)	75.58 ± 29.47	91.09 ± 17.36	105.87 ± 25.37	2.63, 0.01*	4.80, 0.00*	2.66, 0.01*
Cu (ug/dL)	117.13 ± 45.76	136.63± 26.03	155.81± 36.45	2.34, 0.02*	4.03, 0.01*	2.16, 0.03*
Zn (ug/dL)	97.55 ± 38.11	113.79± 21.68	108.26 ± 10.20	1.26, 0.21	1.50, 0.13	2.16, 0.03*
Se (ug/dL)	58.83 ± 54.57	81.98± 21.37	76.81 ± 14.99	1.08, 0.28	1.50, 0.13	1.97, 0.05*

Cca vs C = Cervical cancer patients compared with healthy control
Bca vs C = Breast cancer patients compared with healthy control
Cca vs Bca = Cervical cancer patients compared with healthy control

Table 2: Comparison (Mean±SD) of plasma essential trace elements in stage 2 cervical cancer patients and stage 2 breast cancer patients

Patients	Fe (µg/dl)	Cu (µg/dl)	Zn (µg/dl)	Se (µg/dl)
Cervical cancer (n = 21)	90.56 ± 17.87	135.78 ± 26.77	113.08 ± 22.30	78.24 ± 22.13
Breast cancer (n = 22)	75.78 ± 18.13	113.63 ± 27.20	94.63 ± 22.66	26.52 ± 28.78
t-, p- values	2.69, 0.01	2.68, 0.01	2.69, 0.01	6.58, 0.00

DISCUSSION

Trace elements are important as active centers of enzymes or bioactive substances and excess or deficiency of trace elements potentially lead to several chronic diseases, including cancer by influencing

proliferation, inflammation, apoptosis or disrupting balance between free radicals and antioxidants.[4] Inflammation was proposed as the basis for the development of many cancers[13] as there are evidence associating trace elements with systemic inflammation.[14] Apart from this, the known functions of Cu, Zn, Se and Fe elucidate their possible cancer involvement.[15] The most important functions of trace elements in carcinogenesis are cellular oxygen use, optimising cell membrane integrity and free radical removal through cascaded actions of Cu-Zn-superoxide dismutase, Se-glutathione peroxidases and Cu-Fe-catalase.[5,6] When the removal of free radical is efficient, the integrity of membrane is maintained and thus, the risk of cancer decreases.[13,14] Our present study shows decreased Cu and Fe levels (significantly) or Se and Zn (insignificantly) in breast- or cervical-cancer patients compared with control. Apart from considerable metabolic disturbances and morphological changes caused by imbalances of trace elements, immune function disturbances could also ensue.[16]

The role of Se in reducing the risk of a variety of malignancies was evidenced. Selenium binding proteins include albumin, glutathione peroxidase and thioredoxin reductases which are mainregulators of cellular redox balance.[6] Therefore, the reduction in selenium concentrations might explain decreases in selenoproteins (selenoprotein-P fractions, GSHP or albumin). Reduction in circulating albumin was reported in breast and cervical cancer patients.[17] The selenoproteins function as antioxidant to protect from DNA damage and thus tumour onset. Reports have demonstrated low Se status with risk of cancer development.[18] On the contrary, others found no relationship between cancer development and Se intake.[19] Tissue analyses revealed significantly higher Se concentrations in breast cancer tumours as compared to adjacent healthy tissue.[20] Therefore, low plasma Se concentrations in our cancer patients might be related to high Se tumor tissue level, indicating a Se redistribution. The accumulation of tumor Se was explained.[21] Cancer cells especially breast cancers attract and uptake Se using solute carrier family 7 member 11 (SLC7A11). Moreover, there was over-expression of selenophosphate synthase 2 (SEPHS2) necessary for selenium-protein synthesis in breast cancer tissue.[21] The utilisation of oxygen and DNA synthesis are important functions of Fe.[20] But, high Fe concentrations cause lipid peroxidation and cell death via ferroptosis. Also, Fe overload favours tumour development[22] which varies with tissue type and cancer advancement.[20] Previous studies explained that Fe concentrations is controlled by expression levels of Fe-regulatory proteins/Fe-related genes.[5] Additionally, tumor-associated macrophage (TAM) was reported to provide tumor cells with Fe for cancer cells division, growth, and survival.[23] It was postulated that inflammation cytokines induce synthesis of lactoferrin and ferritin, which remove iron from transferrin. It has been shown that inflammatory process is a common occurrence in cancer patients[24,25], thus reduced circulation Fe as seen in the present cancer patients. Low serum iron may be helpful to the host by impoverish microorganisms of free Fe for multiplication and development and also by reducing free radical production. On the other hand, Fe deficiency has been shown to be disadvantageous to the host through impairment of lymphocyte (B- or T-cell) proliferation and functions.[26] Inflammation cytokine increases circulating hepcidin, which degrades ferroportin Fe export channels[27] to cause restriction of Fe availability but upregulation of Fe in certain phagocytes. This mechanism also explains reduced circulating Fe levels in our cancer patients. It is well established that iron is a negative acute-phase reactant while cancer exhibits an acute phase response, thus reduced level of Fe is expected in cancer patients.

Copper (Cu) is essential for the production of hemoglobin, myelin, collagen, and melanin. Also, Cu-dependent enzymes are important in cellular oxygen usage, Fe balance, and blood vessel formation. High serum Cu and tumour tissue levels were reported in cancer patients[3,21], but another study found no association of high serum Cu levels with increased cancer risk.[27] Moreover, a study revealed no difference in Cu level of breast cancer patient compared to normal breast tissue.[9] Reduced plasma Cu is found in cancer patients considered in this study. Reduced Cu in cancer patients is a disadvantage because Cu supports immune functions.[27]

Zn is crucial for effective immune responses and cell cycle regulation[29,30], which are involved in cancer development and progression. Previous studies indicated no association[31] or inverse relationship between Zn intake/levels and cancer risks.[32,33] However, elevated Zn levels was found in cancer tissues.[34] The abnormal expression of Zn transporters was associated with reduced serum Zn in most cancer patients.[35] Zinc is an example of negative acute-phase reactant and its uptake is enhanced IL-1 and IL-6by binding Zn with metallotheins.[35] A study reported high tissue Zn concentration at the sites of inflammation[27] suggesting localised role of Zn in tissue regeneration. Most circulating zinc is albumin-bound[36,37] and reduced albumin had been previously reported in cancer patients.[17] Above explanations support low plasma Zn levels observed in our cancer patients. Low zinc concentrations may be advantageous for host protection by reducing Zn available for development

and reproduction.Zn maintains immune homeostasis[29,30], regulates hormone formation[29], cytokines production (especially IL-2 and IFN-γ), Complement system functions and antibody formation.[27,29,37-39] Zn deficiency was found to be responsible for low reactive oxygen species (ROS) production, impaired phagocyte adhesion/chemotaxis, reduced macrophage maturation and activities.[39,40] Zn influences T-cell formation, maturation, and function through thymulin hormone.[27,29] T-cells, IL-2 and IFN-γ are important effectors in cancer control.[41] Therefore, a deficiency of Zn especially in breast cancer patients can cause immune function dys-regulation and thus a significant negative influence on health status.

In conclusion, available data further support a previous suggestion that blood levels of metal varies with different cancers. Thus, a need for differential supplementation based on cancer types when modulation of trace element levels becomes a therapeutic option. Therefore, further studies are needed on the mechanism of how tumour cells modulate trace elements or how several trace elements interfere with each other. Moreover, trace elements and their associated markers should be determined in serum and tumour tissues. These are important to obtain maximum benefits of trace elements as therapeutic supplements in cancer management.

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REFERENCES

1. **Bray F.** Global cancer statistics. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J. Clin. 2018;68(6):394–424.
2. **Jimoh MA,** Arinola GO, Abdus-salam A, Adenipekun A.Systemic inflammation response index (SIRI) and aggregate inflammation systemic index (AISI) in male and female cancers: Implication for gender based immunotherapy. J. of Clin and Exp. Invest.. 2023. 14(4): 1-6.
3. **Lossow K,** Schwarz M and Kipp AP. Are trace element concentrations suitable biomarkers for the diagnosis of cancer? Redox Biol. 2021 Jun;42:101900. doi: 10.1016/j.redox.2021.101900. Epub 2021 Feb 18. PMID: 33642247; PMCID: PMC8113050.
4. **Popescu E** and Stanescu AMA. Trace Elements and Cancer. Mod. Med. 2019, Vol. 26 (4). 169-177
5. **Pfeiffer CM** and Looker A.C. Laboratory methodologies for indicators of iron status: strengths, limitations, and analytical challenges. Am. J. Clin. Nutr. 2017;106(Suppl 6):1606S–1614S.
6. **Agarwal A.** Serum zinc levels as a predictor of severity of acute diarrhea. Indian J. Pediatr. 2018;85(3):179–183.
7. **Marques O.** Iron homeostasis in breast cancer. Canc. Lett. 2014;347(1):1–14.
8. **Naidu B.G.** Multivariate analysis of trace elemental data obtained from blood serum of breast cancer patients using SRXRF. Results Phys. 2019;12:673–680.
9. **Jouybari L.** Copper concentrations in breast cancer: a systematic review and meta-analysis. Curr. Med. Chem. 2019
10. **Feng Y.** Serum copper and zinc levels in breast cancer: a meta-analysis. J. Trace Elem. Med. Biol. 2020;62:126629.
11. **Takatani-Nakase T.** Zinc transporters and the progression of breast cancers. Biol. Pharm. Bull. 2018;41(10):1517–1522.
12. **Stephanie A,** Navarro Nilvera, Thomas E and Rohan S. Trace elements and cancer risk: a review of the epidemiologic evidence, Cancer Causes & Control. 2007 (18); 1: 7–27.
13. **Scrivo R,** Vasile M, Bartosiewicz I andValesini G. Inflammation as "common soil" of the multifactorial diseases. Autoimmun. Rev. 2011.10:369-374.
14. **Deng H** *et al.* The dysregulation of inflammatory pathways triggered by copper exposure. Biol. Trace Elem. Res. 2022:10.1007/s12011-022-03171-0. Google Scholar
15. **Arinola OG** and Charles-Davies MA. Micronutrient levels in the plasma of Nigerian females with breast cancer. Afr. J. Biotech. 2008; 7(11):1620-1623.

16. **Arinola OG** and Edem VF. Levels of Interleukin-8 and Catalase Have Correlations with Zinc in Healthy Adults: Implications for Inflammatory Conditions. Ann. Med. Res. 2021; 28(11): 1957-1960.
17. **Jimoh MA** and Arinola OG. Immune-nutritional indices in female Nigerian breast cancer patients with different tumour characteristics. J. Bas.Appl.Res. Biomed., 2023;9(1), 5–8.
18. **Hughes D.J.** Selenium status is associated with colorectal cancer risk in the European prospective investigation of cancer and nutrition cohort. Int. J. Canc. 2015;136(5):1149–1161.
19. **Vinceti M.** Selenium for preventing cancer. Cochrane Database Syst. Rev. 2014;(3).
20. **Jablonska E.** Cadmium, arsenic, selenium and iron- Implications for tumor progression in breast cancer. Environ. Toxicol. Pharmacol. 2017;53: 151–157.
21. **Nunziata C.** Structural analysis of human SEPHS2 protein, a selenocysteine machinery component, over-expressed in triple negative breast cancer. Sci. Rep. 2019;9(1):16131..
22. **Jayachandran A.** Association between hereditary hemochromatosis and hepatocellular carcinoma: a comprehensive review. Hepatoma Res. 2020;6. 8-22.
23. **Duan X.** Tumor associated macrophages deliver iron to tumor cells via Lcn2. Int. J. Physiol. Pathophysiol. Pharmacol. 2018;10(2):105–114.
24. **Jimoh M.A,** Edem VF and Arinola OG. Immune cell counts, systemic immune inflammation index and pan inflammation immune value in female Nigerian breast cancer patients before treatment. Asia J of Imm. 2023; 6 (1): 112-119.
25. **Jimoh M.A** and Arinola OG.Differentiating potentials of pre-treatment blood-cell-based ýnflammation indices inNigeria breast cancer patients. Trop. J. Health Sciences. 2023; 30: 9-13.
26. **Jiang Y,** Li C, Wu Q, *et al.* Iron-dependent histone 3 lysine 9 demethylation controls B cell proliferation and humoral immune responses. Nat. Commun. 2019.10: 2935.
27. **Weyh C,** Krüger K, Peeling P, Castell L. The Role of Minerals in the Optimal Functioning of the Immune System. Nutrients. 2022; 14(3):644.
28. **Stepien M.** Circulating copper and zinc levels and risk of hepatobiliary cancers in Europeans. Br. J. Canc. 2017;116(5):688–696.
29. **Prasad A.S.** Zinc in human health: Effect of zinc on immune cells. Mol. Med.2008;14: 353–357..
30. **Chasapis C.T.** Recent aspects of the effects of zinc on human health. Arch. Toxicol. 2020;94(5): 1443–1460.
31. **Qu X.** Serum zinc levels and multiple health outcomes: implications for zinc-based biomaterials. Bioact Mater. 2020;5(2):410–422.
32. **Stepien M.** Pre-diagnostic copper and zinc biomarkers and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition cohort. Carcinogenesis. 2017;38(7): 699–707.
33. **Stepien M.** Circulating copper and zinc levels and risk of hepatobiliary cancers in Europeans. Br. J. Canc. 2017;116(5):688–696.
34. **Rusch P.** Zinc distribution within breast cancer tissue of different intrinsic subtypes. Arch. Gynecol. Obstet. 2020; 303: 195-205
35. **Takatani-Nakase T.** Zinc transporters and the progression of breast cancers. Biol. Pharm. Bull. 2018;41(10):1517–1522.
36. **To P.K.** Growth modulatory role of zinc in prostate cancer and application to cancer therapeutics. Int. J. Mol. Sci. 2020;21(8): 2991-3005.
37. **Rink L** and Gabriel P. Zinc and the immune system. Proc. Nutr. Soc.2000;59: 541–552.
38. **Haase H,** Rink L. Zinc signals and immune function. BioFactors2014;40: 27–40.
39. **Arinola O.G** and Edem V.F. Correlation of plasma Zinc with neutralising antioxidant enzymes and cellular immune responses in healthy Nigerian adults. Medical Journal of Zambia. 2020; 47(4): 261-268.
40. **Bonaventura P,** Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. Autoimmun. Rev.2015;14:277–285.
41. **Arinola GO,** Edem FV, Odetunde AB, *et al.* Serum inflammation biomarkers and micronutrient Levels in Nigerian breast cancer patients with different hormonal immunohisto-chemistry status. Arch Breast Cancer. 2021; 16(4):355-364.