Tropical Journal of Obstetrics & Gynaecology
ISSN-Print: 0189-5117
Online: 2543-148X
Official Publication of Society of Obstetrics & Gynaecology of Nigeria

■ Original Research Article

Essential- (Cobalt, Chromium, Molybdenium and Nickel) And Non-Essential- (Aluminium, Beryllium and Boron) Heavy Metals in Patients with Breast- or Cervical- Cancer.

Jimoh Mutiu Alani[1], Edem Fabian Victory[2], Arinola Ganiyu Olatunbosun[3]

1.Department of Radiation Oncology, University of Ibadan and University College Hospital, Ibadan, Nigeria. 2. Department of Immunology, University of Ibadan, Nigeria. 3. Faculty of Basic Medical Sciences, KolaDaisi University, Ibadan.

ABSTRACT

Background: There are 23 heavy metals with wide environmental distribution and they are known to induce multiple organ damage even at low levels of exposure. Despite the high degree of toxicity and public health significance of heavy metals, their toxicity depends on their dose, route, host age, gender or organ type. However, Nickel, Chromium, Cobalt, Beryllium, Molybdenum, Boron and Aluminium are less studied in cancers. **Objectives:** To determine the plasma concentrations of essential (cobalt, chromium, molybdenum and nickel) and non-essential (aluminium, beryllium and boron) heavy metals in Nigerian females with breast cancer or cervical cancer. **Method:** This study was undertaken to determine plasma cobalt, chromium, molybdenum, nickel, aluminium, beryllium, nickel and boron in 30 breast cancer patients and 30 cervical cancer patients attending University Teaching Hospital, Ibadan, Nigeria; and 30 healthy female control using Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES). Descriptive statistics was done, with statistical significance set at $p \leq 0.05$. **Results:** The mean plasma cobalt, chromium, molybdenum, nickel, aluminium, beryllium, nickel and boron were not significantly increased in cervical cancer patients or significantly decreased in breast cancer patients compared with healthy female control. However, the mean plasma cobalt, chromium, molybdenum, nickel, aluminium, beryllium and boron were significantly increased in cervical cancer patients compared with breast cancer patients. When stage 2 cervical cancer patients was compared with stage 2 of breast cancer, the mean plasma cobalt, chromium, molybdenum, nickel, aluminium, beryllium and boron were significantly increased in cervical cancer patients compared with stage 2 breast cancer patients. **Conclusion:** This study revealed that concentrations of heavy metals vary with cancer types. Therefore, differential nutritional supports and chelation therapy for the management of cancer patients will be needed for different cancers.

Keywords: Carcinogenicity, Female cancers, Heavy metals, Mechanistic action, Nutritional support.

Correspondence

Arinola Ganiyu Olatunbosun
Department of Immunology, University of Ibadan, Nigeria and Faculty of Basic Medical Sciences, KolaDaisi University, Ibadan.
+234-80-98121520

INTRODUCTION

Heavy metals are metallic elements with a relatively high density compared to water and induce toxicity at low level of exposure.[1]Increasing industrial, agricultural, domestic and technological applications have led to inevitable human exposure to these metals[2] causing toxicity of varied gravities in different organs and gender.[1] Generally, heavy metals can be classified into essential- and non-essential- heavy metals. Essential heavy metals play important roles in human biological functions such as metabolic function, oxidative stress regulation, and embryonic

development. Non-essential heavy metals are harmful to health even at low concentrations and have no established biological functions.[3]The most widely studied heavy metals in relations to cancers are lead, mercury, arsenic, cadmium, antimony and radium[4, 5] while cobalt, chromium, molybdenum, nickel, aluminium, beryllium and boron are relatively less studied. In this study, we determined the plasma concentrations of "neglected" heavy metals [essential (cobalt, chromium, molybdenum and nickel) and non-essential (aluminium, beryllium and boron)]in female patients having breast- or cervical- cancer, so as to increase our knowledge on better management, pathogenesis and prevention of cancers.

Generally, heavy metal induced toxicity and carcinogenicity through many mechanistic aspects, some of which are not clearly elucidated. Several studies have demonstrated that reactive oxygen species (ROS) and oxidative stress which induce multiple organ damage, even at lower levels of exposure play a key role in the toxicity of metals.[1,6] Inflammation, microbiomes, oxidative stress, metals and micronutrients underlie cancer susceptibility and progression. Cancer patients are characterized by a variety of perturbations in homeostasis of metal ions such as zinc, iron, selenium and copper both at intratumoral or systemic level, and studies have shown that metal dysregulation triggers neoplastic transformation of cells.[5-8] Also, epigenetic changes via chromatin immunoprecipitation sequencing, DNA methylation and bisulphite sequencing were implicated in cancers.[8, 9]

Apart from the fact that bio-accumulated toxic elements interact with DNA leading to cell cycle modulation, carcinogenesis or apoptosis, heavy metals also cause diversity of toxic effects on a variety of cellular organelles, enzymes, body tissues and organs to disrupt growth, proliferation, differentiation, damage-repairing processes, and apoptosis.[10]Therefore, suggesting the involvement of "neglected" heavy metals in carcinogenesis. The authors of the present study therefore aimed to assess the plasma concentrations of "neglected" heavy metals in two female gynaecological cancers, so as to improve their managements.

MATERIALS AND METHODS

Thirty (30) cervical cancer patients, 30 breast cancer patients and 30 age matched females without cancer as control subjects were recruited for this study. This was a case-control study where all patients were not on any treatment and were voluntarily recruited at random during visit to the clinic. Patient socio-demographic information is given in Table 1. Ethical approval for the study was obtained from joint University of Ibadan and University College Hospital, Ibadan, Nigeria Research Ethics Committee (UI/EC/23/0065). Plasma separated from five (5) ml of venous blood plasma was analysed for the concentrations of essential (cobalt, chromium, molybdenum and nickel) and non-essential (aluminium, beryllium and boron) heavy metals using 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 using Student *t*-test. $p \leq 0.05$ was taken as significant.

RESULTS

The mean plasma cobalt, chromium, molybdenum, nickel, aluminium, beryllium and boron were non-

Table 1: Sociodemographic Characteristics of Breast Cancer Patients.

Variable	Percentage
Age distribution at diagnosis:	
≤30	3.3%
≥30	96.7%
Educational status:	
Below Tertiary	70%
Tertiary	30%
Marital status:	
Single	3.3%)
Married	73.6%
Divorced	9.9%
Separated	3.3%
Widow	9.9%
Parity:	
Nulliparity	9.9%
Multiparity	36.7%
Grand multiparity	53.3%
Blood Pressure measurements range (mmHg):	
Systolic blood pressure	90-190
Diastolic blood pressure	25-120
Body Mass Index range (Kg/m^2):	19.1-39.0
Menopausal Status:	
Menopausal	53.3%
Premenopausal	46.7%

Table 2: Comparison Of Mean ± S.D Of Heavy Metals In Cervical Cancer With Breast Cancer Patients And Control.

Variables	Breast Cancer (n=30)	Cervical Cancer (n=30)	Control (n=30)
Ni(nmol/L)	0.73 ± 0.70	1.02 ±0.27*	0.95 ± 0.19
Cr (µg/L)	0.530 ± 0.520	0.740 ± 0.190*	0.700 ± 0.140
Co(µg/dL)	0.099 ±0.040	0.210 ± 0.11*	0.160 ± 0.15
Be(ug/dL)	0.05 ± 0.04	0.07 ±0.02*	001 ± 0.001
Mo(ug/dL)	0.05 ± 0.05	0.07 ± 0.01*	0.07 ± 0.01
Bo(ug/dL)	21 ± 3	29 ± 8*	27 ± 5
Al(ug/dL)	1.32 ±1.30	1.84 ± 0.48*	1.73 ± 0.34

*Significantly different between cervical cancer and breast cancer

Table 3: Comparison of Mean ± S.D of heavy metals in stage 2 cervical cancer with stage 2 breast cancer patients

Heavy metals	Cervical cancer (n=21) Mean±S.D	Breast cancer (22) Mean±S.D
Ni(nmol/L)	0.97± 0.28	0.33 ± 0.32*
Cr(µg/L)	0.710 ± 0.20	0.240 ± 0.22*
Co(µg/dL)	0.078 ± 0.02	0.260 ± 0.29*
Be(ug/dL)	0.06 ± 0.02	0.02 ± 0.02*
Mo(ug/dL)	0.07 ± 0 .02	0 .03 ± 0.03*
Bo(ug/dL)	28 ± 8	10 ± 1*
Al(ug/dL)	1.76 ± 0.50	0.60 ± 0.60*

*Significantly different from stage 2 of cervical cancer patients

significantly increased in cervical cancer patients and non-significantly decreased in breast cancer patients compared with healthy female control. However, the mean plasma cobalt, chromium, molybdenum, nickel, aluminium, beryllium and boron were significantly increased in cervical cancer patients compared with breast cancer patients (Table 2). Because of the few numbers of stages 1 and 3 in breast- and cervical-cancer patients considered for this study, heavy metals in only stage 2 of breast cancer patients were compared with stage 2 of cervical cancer patients. The mean level of cobalt, chromium, molybdenum, nickel, aluminium, beryllium and boron were significantly increased in stage 2 cervical cancer patients compared with stage 2 breast cancer patients (Table 3).

DISCUSSION

Heavy metals exhibit an immense bio-accumulating range of toxic effects with regard to carcinogenesis.[1-5]Therefore, effective educational programs are needed to raise awareness of the risks associated with exposure to heavy metals. It is a known fact that the mechanism of heavy metal toxicity varies widely. Also, cobalt, chromium, molybdenum, nickel, aluminium, beryllium, nickel and boron are lessstudied in relation to cancers. Therefore, the reason for the execution of present study. Advances in boron anticancer effort includes a wide-scale application in Boron Neutron Capture Therapy (BNCT), a radiotherapy based of high boron uptake capacity by cancer cells.[10-12]The present study observed raised level of boron in cervical cancer patients. A previous study reported that boron activity during carcinogenesis are inhibition of a serine proteases and NAD-dehydrogenases activities, mRNA splicing, cell division, receptor binding mimicry, and the induction of apoptosis.[13]

Although aluminium has no known biological function, but wide exposure to aluminium[14]make its contribution to cancer a possibility. The fact that aluminiumlevel was increased in cervical cancer patients compared with breast cancer patients or healthy control is an indication thataluminium contributes to carcinogenesis varies with organs. Aluminium is excreted primarily through urine with a very small amount in faeces.[15] It is therefore likely thataluminium is excreted more by breast cancer patients than cervical cancer patients, thus recommending a search into the urine concentration of aluminium in these groups of patients. Aluminium is a toxic non-essential metal inhibiting hexokinase, phosphodiesterase, alkaline phosphatase and phosphoxidase due to its greater affinity to DNA and RNA.[16]Aluminium imbalance causes nausea, vomiting, diarrhea, loss of memory and loss of co-ordination.[17, 18]Since vomiting and diarrhoea results to electrolyte dysregulation, it is therefore likely that dys-electrolyteamia observed in cancer patients might have aluminium-based mechanism.

Chromium exposure damages respiratory, kidney, liver, circulatory and nerve tissues but the main health problems associated with chromium toxicity is with the reproductive system.[19, 20]Thus, supporting increased chromium level seen in cervical patients.[21]Chromium toxicity leads to chromosomal abnormalities, DNA strand breaks[22]and disruption of cellular integrity and functions[23] but the gravity of this varies with chromium sub-types(Cr1-4).[24] Future study into plasma concentrations of chromium sub-types (Cr1- Cr4) in cancer patients will be beneficial. Nickel promotes hypoxia inducing factor (HIF)-α and chromosomal aberrations.[25, 26]Global DNA hypo-methylation and gene-specific hyper-methylation are found in nickel carcinogenesis.[27, 28] Epidemiological studies have revealed a significant correlation between nickel exposure and the incidence of carcinogenesis in breast and ovary[29-32], therefore supporting the involvement of nickel level in breast- and cervical-cancers as shown by the results of present study.

Inhalation through occupational exposure is the main route of beryllium-human contact, but there is little conclusive evidence to suggest that exposure to either beryllium-salts or beryllium-metal particles lead to genotoxicity.[33]Beryllium bind MHC-peptide complex which recogniseCD4+ T-cell receptors to initiate hyperactive response[34]and autoimmune phonomenon.[35]This, therefore provide basis to investigate autoimmune and hypersensitivity in cancer

patients. In experimental animals, beryllium causes adenocarcinomas, osteosarcomas and produced chromosomal breaks[35] and inhibition of DNA repair synthesis[36], thus contributing to cervical cancer as shown in this study.

Different epidemiological studies provide relatively sparse and contradictory data on the carcinogenicity of cobalt to humans.[37, 38] The result of this present study shows no significant differences in the levels of cobalt in cancer patients and unaffected control. Cobalt mimic estradiol by binding to and activating estrogen receptor-alpha.[38]Therefore, involvement of cobalt in female cancers may not be doubtful.

According to Huang *et al*[39] molybdenum is an essential trace element mainly stored in the liver, kidneys, glands and bones. It is also present in the lungs, spleen, skin and muscles. Problems caused by the shortage of molybdenum include intellectual disability, seizures, severe hypertension, tachycardia, nausea, vomiting and coma. Too much molybdenum can cause symptoms similar to gout and other problems involving the gastrointestinal tract, liver and kidneys. Free molybdenum combines with the four sulphur atoms to form tetra-thiomolybdate, which in turn reduces circulating copper and copper dependent binding proteins. Thus, excess molybdenum as seen in cervical cancer patients is unhealthy.

CONCLUSION

Considering the varied concentrations of "neglected" heavy metals in different cancer types, nutritional supports and chelation therapy for the management of cancer patients may be individualised. Because of relatively small number of cancer cases, the results must be interpreted with caution. However, further search for agents to mitigate carcinogenic potential of heavy metals will be beneficial as a new protective target to cancers.

Strength of the study: The study is extensive since it involved 7 "neglected" heavy metals on two different female cancers.

Limitations of the Study: The study was limited because of its small sample size which inhibits comparison between different cancer stages.

Funding sources: Nil

Conflict of interest: Nil

REFERENCES

1. Luo L., Wang B., Jiang J., Huang Q., Yu Z., Li H., et al. Heavy metal contaminations in herbal medicines: determination of comprehensive risk assessments. Front. Pharmacol.2020;11, 595335. 10.3389/fphar.2020.595335 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. He ZL, Yang XE, Stoffella PJ. Trace elements in agroecosystems and impacts on the environment. J Trace Elem Med Biol. 2005;19(2–3):125–140. [PubMed] [Google Scholar]
3. Gazwi H. S. S., Yassien E. E., Hassan H. M. Mitigation of lead neurotoxicity by the ethanolic extract of Laurus leaf in rats. Ecotoxicol. Environ Safe.2020; 192. 110297. 10.1016/j.ecoenv.2020.110297 [PubMed] [CrossRef] [Google Scholar]
4. Sutton D, Tchounwou PB, Ninashvili N, Shen E. Mercury induces cytotoxicity, and transcriptionally activates stress genes in human liver carcinoma cells. Intl J Mol Sci. 2002;3(9):965–984. [Google Scholar]
5. Wang S, Shi X. Molecular mechanisms of metal toxicity and carcinogenesis. Mol Cell Biochem. 2001;222:3–9. [PubMed] [Google Scholar]
6. Arruti A, Fernández-Olmo I, Irabien A. Evaluation of the contribution of local sources to trace metals levels in urban PM2.5 and PM10 in the Cantabria region (Northern Spain) J Environ Monit. 2010;12(7):1451–1458. [PubMed] [Google Scholar]
7. Rockhill B, Spiegelman D, Byrne C, Hunter, D J. & Colditz, G. A. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. J. Natl. Cancer Inst. 2001;93: 358–466.
8. Akinmoladun VI, Edem FV, Popoola OA and Arinola OG. Global DNA Methylation Profile of Head and Neck Squamous Carcinoma Patients at the University College Hospital, Ibadan, Nigeria. Intl Res J Oncol. 2020; 3(2): 13-19.
9. Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. Arch Toxicol. 2008;82(8):493–512. [PubMed] [Google Scholar]
10. Cebeci E, Yüksel B, Şahin F. Anti-cancer effect of boron derivatives on small-cell lung cancer. Journal of Trace Elements in Medicine and Biology. 2022;Mar;70:126923. doi: 10.1016/j.jtemb.2022.126923. Epub 2022 Jan 4. PMID: 35007916.
11. Kulkarni S, Bhandary D, YogeshSingh, VikramdeepMonga, SureshTharejaBoron in cancer therapeutics: An overview. Pharma & Therap.2023; 251, November 2023, 108548.
12. Borek B, Gajda T, Golebiowski A, Blaszczyk R. Boronic acid-based arginase inhibitors in cancer immunotherapy. Bioorg Med Chem. 2020 Sep 15;28(18):115658. doi: 10.1016/j.bmc.2020.115658. Epub 2020 Jul 23. PMID: 32828425.
13. Scorei RI, Popa R Jr. Boron-containing compounds as preventive and chemotherapeutic agents for cancer. Anticancer Agents Med Chem. 2010; May10(4):346-51. doi: 10.2174/187152010791162289. PMID: 19912103.
14. Martinez-Finley EJ, Chakraborty S, Fretham SJ, Aschner M. Cellular transport and homeostasis of essential and nonessential metals. Metallomics. 2012 Jul;4(7):593-605. doi: 10.1039/c2mt00185c. Epub 2012 Feb 15. PMID: 22337135; PMCID: PMC4936191
15. Priest ND. The biological behaviour and bioavailability of aluminium in man, with special reference to studies employing aluminium-26 as a tracer: review and study update. J Environ Monit. 2004 May;6(5):375-403. doi: 10.1039/b314329p. Epub 2004 Apr 23. PMID: 15152306.

16. Olaniran AO, Balgobind A, Pillay B. Bioavailability of heavy metals in soil: impact on microbial biodegradation of organic compounds and possible improvement strategies. Int J Mol Sci. 2013;14(5):10197–10228. [PMC free article] [PubMed] [Google Scholar]
17. Kochian LV, Piñeros MA, Hoekenga OA. The physiology, genetics and molecular biology of plant aluminum resistance and toxicity. Plant and Soil. 2005;274:175–195. [Google Scholar]
18. Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J, Rondeau V. Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. JJ Toxicol Environ Health B Crit Rev. 2007;10(S1):1–269. [PMC free article] [PubMed] [Google Scholar]
19. United States Pharmacopeia General Chapter 232 Elemental Impurities – Limits: First Supplement to USP 40–NF 35, 2017, https://www.usp.org/chemical-medicines/elemental-impurities-updates
20. Cooper AM, Felix D, Alcantara, F, Zaslavsky I, Work A, Watson PL, Pezzoli K, Yu Q, Zhu D, Scavo AJ, Zarabi Y, and Schroeder JI. Monitoring and mitigation of toxic heavy metals and arsenic accumulation in food crops: A case study of an urban community garden. Plant Direct. 2020;4:1-12. doi: 10.1002/pld3.198
21. Akün, ME. Heavy Metal Contamination and Remediation of Water and Soil with Case Studies from Cyprus. In: Heavy Metal Toxicity in Public Health; 2020, DOI: 10.5772/intechopen.90060
22. Aggarwal V., Tuli H., Varol A., Thakral F.,Yerer M., Sak K., *et al*. Role of reactive oxygen species in cancer progression: molecular mechanisms and recent advancements. Biomolecules. 2019;9 (11), 735. 10.3390/biom9110735 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
23. Pavesi T., Moreira J. C.Mechanisms and individuality in chromium toxicity in humans. J. Appl. Toxicol.2020; 40, 1183–1197. 10.1002/jat.3965 [PubMed] [CrossRef] [Google Scholar]
24. Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR, Sadeghi M. Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic. Front Pharmacol. 2021 Apr 13;12:643972. doi: 10.3389/fphar.2021.643972. PMID: 33927623; PMCID: PMC8078867.
25. Harai R, Harari F, Forastiere F. Environmental nickel exposure from oil refinery emissions: A case study in Ecudor. Annalidell'IstitutoSuperiore di Sanità. 2016;52(4):495-499. DOI: 10.4415/ANN_16_04_06
26. Ma L, Bai Y, Pu H, Gou F, Dai M, Wang H, He J, Zheng T, Cheng N. Histone methylation in nickel-smelting industrial workers. Plos One. 2015;19(10). DOI: 10.1371/journal.pone.0140339
27. Linhart C, Talasz H, Morandi EM, et al. Use of underarm cosmetic products in relation to risk of breast cancer: A case-control study. EBioMedicine. 2017;21:79-85. doi: S2352-3964(17)30233-5 [pii].
28. Gopal R, Narmada S, Vijayakumar R, Jaleel CA.
29. Chelating efficacy of CaNa2 EDTA on nickel-induced toxicity in Cirrhinusmrigala (Ham.) through its effects on glutathione peroxidase, reduced glutathione and lipid peroxidation. ComptesRendusBiologies. 2009;332(8):685-696. DOI: 10.1016/j.crvi.2009.03.004.
30. Huang H, Zhu J, Li Y, Zhang L, Gu J, Xie Q, Jin H, Che X, Huang C, Chen LC, Lyu J, Gao J, Huang C. Up regulation of SQSTM1/p62 contributes to nickel-induced malignant transformation of human bronchial epithelial cells. Autophagy. 2016;12(10):1687-1703
31. Yu M, Zhang J. Serum and hair nickel levels and breast cancer: Systematic review and meta-analysis. Biological Trace Element Research. 2017:175(2):1-7. DOI: 10.1007/s12011-017-0949-7
32. Yang Y, Jin X, Yan C, Tian Y, Tian J, Sen X. Urinary level of nickel and acute leukemia in Chinese children. Toxicology and Industrial Health. 2008;24(9):603-610. DOI: 10.1177/0748233708100091
33. Darbre PD. Metalloestrogens: An emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. J ApplToxicol. 2006;26(3):191-197. doi: 10.1002/jat.1135 [doi].
34. Strupp C. Beryllium metal I. experimental results on acute oral toxicity, local skin and eye effects, and genotoxicity. Ann OccupHyg. 2011;55:30–42 [PMC free article] [PubMed] [Google Scholar]
35. Dai S, Falta MT, Bowerman NA, McKee AS, Fontenot AP.T-cell recognition of beryllium. CurrOpin Immunol. 2013;25:775–80 [PMC free article] [PubMed] [Google Scholar]
36. Clayton GM, Wang Y, Crawford F, Novikov A, Wimberly BT, *et al*. Structural basis of chronic beryllium disease: linking allergic hypersensitivity and autoimmunity. Cell.2014;158:132–42 [PMC free article] [PubMed] [Google Scholar]
37. Mayer AS, Hamzeh N, Maier LA. Sarcoidosis and chronic beryllium disease: similarities and differences. Semin Respir Crit Care Med35. 2014; 316–329 [PubMed] [Google Scholar]
38. Moulin JJ, Wild P, Romazini S, Lasfargues G, Peltier A, Bozec C, et al. Lung cancer risk on hard-metal workers. Am J Epidemiol. 1998;148:241–248.
39. Jacob K.Kresovich, SerapErdal, Hua Yun Chen, Peter H. Gann. Maria Argos, Garth H. Rauscher. Metallic air pollutants and breast cancer heterogeneity, Environmental ResearchVolume 177, October 2019, 108639.
40. Huang XY, Hu DW, Zhao FJ. Molybdenum: More than an essential element. J Exp Bot. 2022 Mar 15;73(6):1766-1774. doi: 10.1093/jxb/erab534. PMID: 34864981.