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LEVEL OF ZINC AND CADMIUM IN SERUM OF CIGARRETTE SMOKER AND THE RISK OF THE PROSTATE CANCER, KHARTOUM STATE

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Abstract

Background: Tobacco smoke contains many oxidant s and free radicals that can cause damage to lipids, proteins, DNA, carbohydrates and other biomolecules. This is a case-control study. Carried out in Khartoum State from December to February 2015.

Material and Method: Three ml of venous blood were collected from study population; serum zinc and cadmium was estimated using absorption spectrophotometer.

Results: The study results revealed that the mean age of smokers was (26.7±6.3) year and for non smokers was (25.0±7.0) year. The mean±SD of serum zinc and cadmium in smokers respectively were 0.51±0.22 and 0.08±0.040 µg/L. The mean±SD of serum zinc and cadmium in non-smokers were 0.65±0.21and 0.0002±0.0001µg/L respectively. There was a highly significant difference in serum zinc between smokers and non-smokers (p value 0.000, <0.05. Cadmium was significantly higher in smokers compared with non-smokers ($p<0.05$), the level in smokers being four (4) fold than in non-smokers. In contrast Zn level was significantly reduced in smokers compared with non-smokers ($p<0.05$). However the Zn was significantly higher in non- smokers than in smokers ($p<0.05$). The zinc: cadmium ratio was significantly reduced ($p<0.001$), implying high cadmium: zinc ratio. This ratio was (8.7) times the level in non-smokers. Correlation studies showed negative significant association between Zn and number of cigarette per day ($r= -0.748$, $p<0.01$) and between duration of smoking were strongly positively correlated ($r= 0.297$, $p< 0.05$). Also significantly positive correlation between Cd and number of cigarettes per day($r= 0.947$, $p< 0.01$) and negative correlation with duration of smoking in years ($r= -0.422$, $p< 0.01$).

Conclusion: This study concluded that; level of serum cadmium is increased in cigarette smokers and serum zinc decreased. The increased in level of serum cadmium affected by the duration of smoking and number of cigarettes smoked per day. This study appears to provide evidence to show that the convergence of: reduced Zn level, high Cd: Zn ratio, may serve as a simple panel of biomarkers of risk of prostate cancer.

Keywords: Cigarette Smoker's Serum Zinc, Serum Cadmium, Khartoum State, Prostate Cancer

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INTRODUCTION

Smoking is single greater cause of preventable death globally. Smoking lead to disease affect heart, liver and lung (World health organization, 2008). Which can lead to heart attack, stroke, chronic obstructive pulmonary disease, peripheral vascular disease and hypertension. (Vainio, 1987) Smoke contains several carcinogenic paralytic that bind to DNA and cause many genetic mutations. (Fowles and Dybing, 2003) Some trace element such as zinc found to be deficient among health smoker compare to nonsmoker. (Basher and Mitra, 2004) And cadmium can increase after inhalation from cigarette smoke, can be as high as 50%. (Schwerha, 2006) The risk of prostate cancer increase with genetic factor which associated with race, family and specific gene variant. Many different gene can be implicated .such as mutation in BRCA1, BRCA2 and HPC1(Whitaker *et al*., 2010) and dietary factor which lead to lower blood level of vitamin D (Wiggle *et al*., 2008) also infection with sexual transmitted virus. (Dennis *et al*., 2002). Some trace element is responsible for increase risk of prostate cancer. For example, alteration of blood concentration of cadmium by increasing and zinc by decreasing can increase risk of prostate cancer. (Leslie, 2006). Levels of zinc to cadmium inhibit the protective effect of zinc on cadmium toxicity. (Parizek, 1957) Lead to increase risk of the potential development of proliferative lesion in the prostate of smoker resulting from inhibition of apoptosis and suppression of DNA repair gene secondary to reduce zinc. (Goyer *et al*., 2004). Zinc is an essential trace element for humans (Marat and Wolfgang, 2013), animals (Prasad, 2008), plant (Broadly *et al*., 2007) and microorganism. (Fosmire, 2009). It is typically the second most abundant transition metal in organism after iron and it is only metal which appear in all enzyme classes (Bothwell *et al*., 2003).

Zinc is an essential requirement for good heath, excess zinc can be harmful. The free zinc ion is powerful Lewis acid up to the point of being corrosive. Stomach acid contain HCL , in which metallic zinc dissolve readily to give corrosive zinc Chloride can cause damage to the stomach due to solubility of the zinc ion in acidic stomach. (Lamore *et al*., 2010) Also high zinc can suppress cupper and iron absorption. (Tampa Bay times, 2013) Deficiency of those make condition called zinc shakes or "zinc chills" also high zinc damage nerve receptor in the nose, which can cause insomnia. (Morrow, 2010). Cadmium has no known useful role in higher organisms. (Lane, 2000) the most dangerous form of occupational exposure to cadmium is inhalation of fine dust and fumes, or ingestion of highly soluble cadmium compounds. (Hogan Michae, 2010) inhalation of cadmium containing fumes can result initially in metal fume fever, but may progress to chemical pneumonitis , pulmonary edema and death. (Morel and François, 2005).

High cadmium associated to higher risk of endometrial, breast and prostate cancer as well as to osteoporosis in human. (Morel and François, 2005) (Nogawa *et al*., 2004) (Angstrom *et al*., 2012) However the current study aimed to measure cadmium and zinc concentration among smoker and non smoker male.

MATERIALS AND METHODS

Study area: The study was conduct in Khartoum state during the period of December 2014 –February 2015.

Study design: The study was case control design.

Sampling selection: Study include 100 health males, 50 smoker and 50 Non smoker males in Khartoum state with age group ranged between 17-45 years.

Inclusion criteria: Smoker male at age between (17-45) years.

Exclusion criteria: The exclusion criteria includes; male with malnutrition, male with any chronic diseases, snuffer user and alcohol consumption male.

Data collection: The data was collected via laboratory examination and questionnaire.

Sample collection: Under a septic condition, about 3ml of venous blood were collected from each volunteer by vein puncture technique and were placed in anticoagulant free containers, and allowed to clot then centrifuged at 3000 rpm for 5 minutes to obtain serum which kept in eppendorf tubes for measurements of Zinc and Cadmium. Serum Zinc and Cadmium were measured by using Atomic Absorption Spectrophotometer.

Ethical consideration: The approval of the research was taken from the ethics review of Alneelain University Post Graduated Program and data was handled with high degree of confidentiality throughout the study.

Statistical Analysis: Statistical evaluation was performed using the Microsoft Office Excel (Microsoft Office Excel for windows; 2007) and SPSS (SPSS for windows version 18). Inferential statistics was used such as student's t-tests and Pearson's correlation.

RESULTS

Table 1. Mean (Mean ± SD) of age, serum chromium and cobalt in smokers and non smokers

Variable	Study group		Significance test
	Smokers (Exposed)	Non-smokers (Control)	P.value
Age (years)	26.7±6.3	25.0±7.0	0.215
Zinc (M ± SD µg/L)	0.51±0.22	0.65±0.21	0.001***
Cadmium (M ± SD µg/L)	0.08±0.040	0.0002±0.0001	0.000***

***P-value significant at 0.05 level

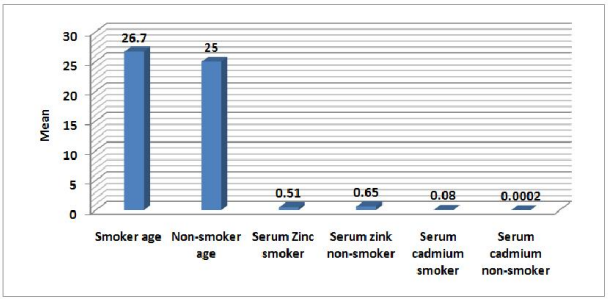

Fig. 1. Mean of age, serum Zinc and cadmium in smokers and non smokers

Table 2 Serum cadmium to serum zinc ratio

	Group	Mean	Std. Deviation	p-value
Cd : Zn ratio	Control	0.0003	0.0002	0.000***
	Smoker	0.261	0.331	

***P-value significant at 0.05 level

DISCUSSION

Cigarette is made up of tobacco, paper and additives. Usually in cigarette manufacture 600-1400 additives are used (Akesson *et al*., 2008). Cigarette smoking is responsible for more than 85% of lung cancers and also cause the mouth, pharynx, larynx, esophagus, stomach, pancreas, kidney, uterine, ureter, bladder and colon cancer. It has also been linked to Leukemia. Apart from the carcinogenic aspects of cigarette smoking, it is also linked to increased risks of cardiovascular diseases, cardiac arrest, peripheral vascular disease; sudden death and aortic aneurysm have also been established. Many components of cigarettes smoke irritate the lining of respiratory system characterized as Ciliotoxic materials. They cause increased bronchial mucus secretion and chronic decreases in mucociliary and pulmonary function (Sierra *et al*., 2004). The results are presented in Tables 1, 2, 3 and figure 1. Our study showed that the participants (smoker and non-smoker) were young (aged < 30 yrs). The finding indicated that smoking habit was predominant among adolescents. The finding is disagreed with Iftikhar *et al*., 2013. (Afridi *et al*., 2009). Total mean value of serum Zinc was lower in smokers than non-smokers, whereas elevation of serum cadmium was observed in smokers as compared to non-smokers. However similar finding was obtained by Iftikhar *et al*., 2013. (Afridi *et al*., 2009). Cadmium was significantly higher in smokers compared with non-smokers ($p<0.05$), the level in smokers being four (4) fold than in non-smokers.

Table 3. Pearson correlation between duration of smoking, no. of cigarette per day, serum zinc and serum cadmium

	Serum Cadmium		Serum zinc	
Variable	Pearson Correlation (R)	Sig. (2-tailed)	Pearson Correlation (R)	Sig. (2-tailed)
Duration in years	0.297*	0.036*	-0.422-**	0.002**
Number of cigarettes/day	0.947**	0.000**	-0.748-**	0.000**

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

In contrast Zn level was significantly reduced in smokers compared with non-smokers ($p<0.05$). However the Zn was significantly higher in non- smokers than in smokers ($p<0.05$). The zinc: cadmium ratio was significantly reduced ($p<0.001$), implying high cadmium: zinc ratio. This ratio was (8.7) times the level in non-smokers. Correlation studies showed negative significant association between Zn and number of cigarette per day ($r= -.748$, $p<0.01$) and between duration of smoking were strongly positively correlated ($r= .297$, $p< 0.05$). Also significantly positive correlation between Cd and number of cigarettes per day($r= .947$, $p< 0.01$) and negative correlation with duration of smoking in years ($r= -.422$, $p< 0.01$). Cigarette smoking represents a source of substantial exposure to cadmium over a prolonged period.

Each stick of cigarette contains 1-2 ug of cadmium of which about 10% is absorbed by the lung. The significantly higher cadmium level found in smokers in this study is consistent with earlier studies that blood cadmium levels for smokers may be up to four times as high as those for those for non smokers (Iftikhar Hussain Bukhari *et al*., 2013) and that because of cadmium's extremely long biological half-life, even ex-smokers have higher Cd levels than non smokers. (Iftikhar Hussain Bukhari *et al*., 2013) and that because of cadmium's extremely long biological half-life, even ex-smokers have higher Cd levels than non smokers. The very significantly decreased Zn level in smokers appears to confirm the known mutual antagonism between zinc and cadmium. (IPCS, 1992). This may be attributed to the competition between Zn and Cd for binding sites on metallothionein. This suggests the strong possibility therefore, that increase in cadmium level diminishes zinc levels in smokers. It is also possible that this arises because of the competition for common metabolic pathways by Cd and Zn.

This observed depression of zinc has far reaching implications for cellular activities and genomic stability and by extension for the pathogenesis of prostate cancer. Zinc is central to DNA repair pathways, perturbation of which may be involved in prostate cancer etiology. Cadmium alters the fidelity of DNA replication (Schümann, 1993), DNA disruptions leads to gene rearrangements, translocations, amplifications and deletions which can contribute to cancer development (Williams *et al*., 2000). Another mechanism by which Cd may participate in the prostate carcinogenic process is by Oxidative stress and attendant oxidative injury. Cadmium is associated with increased generation of reactive oxygen species (ROS) (Pioriet *et al*., 2002). Zinc reverses oxidative damage as a constituent of cytotoxic copper-zinc superoxide dismutase (Cu-Zn SOD) (Pioriet *et al*., 2002). The decreased Zn level may be permissive to DNA oxidative damage which can lead to mutation. Mutation is an important phenomenon in cancers of many sites (Clayson, 2001).

The observed reduced zinc level also appears in line with the hypothesis of Levander and Cheng (1980) (Ho *et al*., 2003) and Mills (1981) who stated that an overabundance of one trace element can interfere with the level and metabolic utilization of another element present in normal or marginal concentrations. This is very important owing to the fundamental role of zinc in DNA and protein synthesis and metabolism (Prasad, 1993). Zinc is essential for prostate function (Kerr *et al*., 1964) and it has been shown that Zinc deficiency results in increased oxidative DNA damage and disruption of the p53 tumour suppressor protein (Ho *et al*, 2003). Though men with very high intake of supplemental zinc had a significant two-fold increased risk of prostate cancer (Krone *et al*., 2001), this is probably due to contamination of Zn supplement with Cd (Krone *et al*., 2001). Cadmium is a very common contaminant of zinc as they occur in the same ore (Iftikhar Hussain Bukhari *et al*., 2013).

Also, the significantly reduced Zn per se, the high Cd: Zn or low Zn: Cd ratio in comparison to non-smokers implies that cellular cadmium burden is substantial. This indicates significantly reduced level of Zn relative to Cd, thus suggestive of the loss or significant inhibition of the overriding protective effect of Zn on cadmium toxicity (Parizek, 1957) leading to a raised Cd burden in a given cellular unit and in turn the intensity or enhancing its effect on cellular processes. This may at least in part increase the risk of the potential of development of proliferative lesion in the prostate of smokers probably concomitant with the greater genome instability. This appears consistent with the very recent observation of Goyer, (Zhou, 2004) that the pathogenesis of prostatic cancer (carcinogenesis) might include aberrant gene expression resulting in stimulation of cell proliferation or inhibition of apoptosis. Suppression of DNA repair secondary to reduced Zn would add to the population of cells with damaged DNA. Thus one consequence of the high cadmium: zinc ratio may be the high error rate and lack of efficient DNA repair systems leading to high mutation rate leading to prostate carcinogenesis.

The ratio of zinc to cadmium concentrations has been so important in some other pathologies that whether an industrial worker is susceptible to hypertension and or coronary heart disease is determined by this ratio (Bosquet, 1979). This has however not been extended to cadmium associated prostatic carcinogenesis. Zinc can sometimes be displaced on the zinc fingers by other divalent metals. Iron, for example has been used to displace zinc on the DNA binding protein that also binds estrogen (Yoko *et al*., 1994). This protein binds to the estrogen response element of the DNA in the promoter regions encoding estrogen responsive gene products. When this occurs in the presence of H_2O_2 and ascorbic acid, damage to the proximate DNA, the estrogen response element occurs. It has been suggested in this circumstance of an iron substituted zinc

finger that free radicals are more readily generated with consequences of genomic damage (Conte *et al*., 1996). This suggestion has been offered as an explanation of how excess iron (iron toxicity) could initiate the cellular changes that occur in carcinogenesis. Similarly, in excess cadmium it can also substitute for zinc in zinc fingers. In this substitution the resultant fingers are nonfunctional, impair DNA repair and function.

Although the prevalence of Zn deficiency is uncertain globally (Sandstead, 1991) it appears commoner among populations of developing countries (Gibson, 1994) where smoking is also on the increase (Anetor and Adeniyi, 2001) while it is on the decline in the developed world. A deficiency of Zn ranks among the top ten leading causes of death in developing countries (WHO, 2002). This may be accentuated by the poor recognition of the importance of zinc (Waalkes *et al*., 1999).
Some studies have also shown an increased concentration of cadmium in prostates with cancer compare to normal glands (Castro *et al*., 1992). This is indirectly consistent with the findings; in this study in that increased plasma Cd concentration will ultimately increase prostatic tissue concentration and owing to the mutual antagonism between both elements, displace Zn. The induced Zn deficiency can lead to DNA disorders (De Kok *et al*., 1988).

Though at present there is lack of agreement on the role of cadmium on prostate cancer in cigarette smokers, alteration of Zn status especially a high ratio of Cd: Zn may be a critical factor but this has not been previously explored. It may however serve as a simple reliable predictive biomarker of the risk of cancer of the prostate in smokers. This study appears to provide evidence to show that the convergence of: reduced Zn level, high Cd: Zn ratio, increased Cu level, decreased total globulin may serve as a simple panel of biomarkers of risk of prostate cancer. This appears reasonably consistent with the conclusion of De Kok *et al*. (1988) who examined serum Cu and Zn levels and risk of death from Cancer and Cardiovascular disease level may greatly increase genome instability and permissive to prostate epithelial proliferation that may culminate in cancer.

Conclusion

This study concluded that; level of serum cadmium is increased in cigarette smokers and serum zinc decreased. The increased in level of serum cadmium affected by the duration of smoking and number of cigarettes smoked per day. This study appears to provide evidence to show that the convergence of: reduced Zn level, high Cd: Zn ratio, may serve as a simple panel of biomarkers of risk of prostate cancer.

REFERENCES

Afridi, H.I. Kazi, T.G. Kazi, N.G. Jamali, M.K. Arain, M.B. 2009. Evaluation of cadmium, lead, nickel and zinc status in biological samples of smokers and nonsmokers hypertensive patients. *Journal of human hypertension,* 24(1): 34-43.

Akesson, A. Julian, B. and Wolk, A. 2008. "Long term dietarycadmium intake and postmenopausal endometrial cancer incidence ". Cancer Research.68:6435-6441.

Anetor, J.I**.**, Ajose, F**.**, Anetor , G.O**.**, Iyanda, A.A**.**, Babalola, O.O**.** and Adeniyi, F.A**.** 2008. High cadmium / zinc ratio in cigarette smokers: potential implications as a biomarker of risk of prostate cancer. *Niger J. Physiol Sci***.,** (1-2):41-9.

Angstrom, A. Michaelsson, K. Vahtor, M., Julian, B., Wolk, A. 2012. Kasson A "association between dietary cadmium exposure and bone mineral density and risk of osteoporosis" Environ Health Perspect;.

Basher, S.K. and Mitra, A.K. 2004. Effect of smoking on vitamin A, vitamin E, and other trace elements in patients with cardiovascular disease in Bangladesh: a cross-sectional study. *Nutr J.,* 3: 18.

Bosquet, W. F. 1979. Cardiovascular and renal effects of cadmium In: Mennear,J. H. A. (ed). Cadmium Toxicity, Marcel Dekker Inc. New York, pp. 133-157.

Bothwell, Dawn, N., Mari, Eris, A. 2003. Cable, Benjamin "chronic ingestion of a zinc –based penny ".

Broadly, M.R., White, P.J., Hammond, J.P., Zelko, I. and Lox, A. 2007. Zinc in plants. New physiologis t; 173: 677.

Castro, C. E., Kaspin, L. C., Chen, S. S. and Nolker, S. G. 1992. Zinc deficiency increases the frequency of single strand DNA breaks in rat liver. Nutr. Res. 12:721-736.

Conte, D. Narindrasorasak, S. and Sarkar, B. 1996. In vivo and in vitro iron replaced zinc finger, generates free radicals and causes DNA damage. *J. Biol. Chem*., 271: 5125 – 5130.

De Kok, L.J., F. Buwulda and W. Bosma, 1988. Determination of cysteine and its accumulation in spinach leaf tissue upon exposure to excess sulfu r. *J. Plant Physiol.,* 133: 502-505.

Dennis, L.K., Lynch, C.F. and Torner, J.C. July 2002. "Epidemiologic association between prostatitis and prostate cancer". Urology 60 (1): 78–83.9.

Fosmire, G.J. 2009. "Zinc toxicity " American Journal of Clinical Nutrition 990; 51(2):225–7."

Fowles, J. and Dybing, E. 2003. ''Application of toxicological risk assessment principle of the chemical constitute of cigarette smoke". Tob Control. Dec;12(4):424-30.

Gibson, R. 1994. Zinc nutrition in developing countries. *Nutr. Res. Rev*. 7:151-73.

Goyer, R. A., Liu J. and Waalkes, M. P. 2004. Cadmium and cancer of the prostate and testes. Biometals. 17:555-558.

Ho, E., Courtemanche, C. and Ames, B. N. 2003. Zinc deficiency induces oxidative DNA damage and increases p53 expression in human lung fibroblast. J. Nutr. 133: 2543 – 2548. 11. 33. 33.

Levander, O. A. and Cheng, L. Micronutrients Interaction: vitamins, minerals and hazardous elements, Ann. (1980). NY Acad. Sci. 355: 1-35.

Hogan. Michael. Heavy metal. Encyclopedia of earth. National council for science and the environment .E. Monsoon and C .Cleveland (eds) .Washington DC. (2010)

Iftikhar Hussain Bukhari, Nabila Rasul, Shazia Kausar , Syed Ali Raza Naqvi, Zulfiqar Ali, Muhammad Riaz. Comparative Studies of Ni, Cd, Mn, Co, Pb, Cr and Zn in Hair, Nail and Plasma of Smokers and Non-smokers Subjects of Sargodha Zone (2013). IJCBS, 4(2013):28-37.

IPCS (International Programme on Chemical Safety). Cadmium, Environmental Health Criteria 134 Geneva: World Health Organization. (1992).

Kerr, W. K., Keresteci, A. G and Mayoni, H. 1964. The distribution of zinc within human prostate. Cancer 13: 5524-5531.

Krone, C. A., Wyse, E. and Ely, J. T. A. 2001. Cadmium in Zinc-containing mineral supplements. *Int. J. Food Sci. Nutr*., 52:379-82.

Lamore, S.D., Cabello, C.M. and Wondrak, G.T. 2010 May. " The topical antimicrobial zinc pyrithionic is heat shock response induce that cause DNA damage and PARP – dependent energy crises in human skin cell". Cell Stress Chaperones. ; 15 (3):309-22.

Lane, Todd W., Saito, Mak, A. George, Graham N., Puckering, 2000. Ingrid J ,prince, roger C,

Leslie, C. Costello and Renty, B. 2006. Franklin. The clinical relevance of the metabolism of prostate cancer; zinc and tumor suppression: connecting the dots. Journal-molecular cancer, review.

Marat, Wolfgang "chapter 12 .zinc and human disease in astrisigle, Helmut Sigel and Rolland K.O. Sigel. (2013).

Mills, C. F. 1981. Interactions between elements in tissues: Studies in animal models. Fed. Pro. c. 40: 2138 – 2143.

Lane, T.W., Saito, M.A., George, G.N., Pickering, I.J., Prince, R.C. and Morel, F. 2005. a cadmium enzyme from a marine diatom. *Nature*. 5;435(7038):42.

Morel and François M.M . "cadmium enzyme for marine diatom". Natl Acad. Sci. USA 97, 4627–4631.

Morrow, H. 2010. "Cadmium and cadmium Alloys" . Kirks-othmer Encyclopedia of chemical technology. Published Online.

Nogawa, K.O.J.I., Kobayshi, E., Okubo,Y. Swazono, Y. "Environmental cadmium exposure, adverse effect and preventative measure in japans "Biometals. 2004 Oct; 17(5):581-7.

Parizek, J. 1957. The destructive effect of cadmium ion on testicular tissue and its prevention by zinc. *J. Endocrinol.* 15:56-63.

Pioriet, M. C. and Weston, A. 2002. DNA damage, DNA repair and mutagenesis. In: Bertino, J.R. (eds). Encylopaedia of Cancer. Boston (MA), Academic Press.

Prasad A.S . 2008. "Zinc in human health ". *Mol Med*., 14(5-6):353-7.

Prasad, A. S. 1993. Zinc and gene expression In: Prasad AS, ed. Biochemistry of Zinc. Plenum Press, New York, pp55-76.

Sandstead, H. H. 1991. Zinc deficiency: a public health problem *J. Dis. Child*. 145:835-859.

Schümann, K. 1993. "Interaction between iron and lead. In: Metal- Metal Interactions". Elsenhans,B, Forth, W. and Schümann,K. (eds).Bertelsmann Foundation Publishers, Gütersloh,Germany, pp. 56-71.

Schwerha, J.J. 2006. Occupational medicine forum. *J Occup Environ Med.*, 48(9):988-990.

Sierra-Torres, M.S. Arboleda-Moreno, Y.Y. Hoyos, L.S. Sierra-Torres. C.H. 2004. Chromosome aberrations among cigarette smokers in Colombia.Mutation Research/Genetic Toxicology and Environmental Mutagenesis. 562(1): 67-75.

Tampa Bay times 2013. Cadmium, lead and zinc contamination on the oyster Crassostrea gigas muscle harvested from the estuary of Lamnyong River, Banda Aceh City, Indonesia. AACL Bioflux, 2015, Volume 8, Issue 1.

Vainio, H. 1987. Passive smoking increase cancer risk. Scand *Jwork environ health* 13(3):193-6.

Waalkes, M. P., Anver M. and Diwan, B. A. 1999. Carcinogenic effects of cadmium in the noble (NBL/Cr) rat: Induction of pituitary, testicular and injection site tumors and intraepithelial proliferative lesions of the dorsolateral prostate. Toxicol. Sci. 52:154-161.

Whitaker, Hayley, C. Zsofia Kote-JaraiHelen Ross-Adams, Anne Y. Warren,4 Johanna Burge, (OCT 13 ,2010). PLoS One v.5(10); 2010. PMC2954177.

WHO (World Health Organization). The World Health Report 2002: Reducing risks, promoting healthy life style. Geneva, Switzerland, WHO.

Wiggle, D.T. Turner, Gomes, J., Parent, M.E. 2008. "Role of hormonal and other factor in human cancer prostate cancer". *J Toxicol Environ Health* (Part A) 11:242-259.

Williams, P. L., James, R. C. and Roberts, S. M. 2000. Chemical Carcinogenesis. In: Principle of Toxicology: Environmental and Industrial Application. John Wiley and Sons Inc. New York, P. 78.

World health organization, 2008. WHO report on the global tobacco epidemic: the MPOWER package. Geneva, World Health Organization.

Yoko, K., Alcock, N. and Sandstead, H. 1994. Iron and zinc nutriture of premeno-pausal women: associations of diet with serum ferritin and plasma zinc disappearance. J. lab. Clin. Med. 124:852-861.

Zhou, T**.**, Jia, X**.**, Chapin, R.E**.**, Maronpot, R.R**.**, Harris, M.W**.**, Liu, J**.**, Waalkes, M.P. and Eddy, E.M**.** 2004. Cadmium at a non-toxic dose alters gene expression in mouse testes. Toxicol Lett. 30; 154(3):191-200.

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