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RESEARCH ARTICLE

ROLE OF CADMIUM AND LEAD IN MALIGNANT BREAST TUMOR DEVELOPMENT

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ABSTRACT

Breast Cancer is the major cause of morbidity and mortality in women globally. Elements involved in Environmental toxicology; are closely related to malignant tumor growth. The aim of this study is to assess the concentration of lead and cadmium in serum as well as in tissues of malignant tumor patients and normal breast patients. The estimation was done by atomic absorption spectrophotometer. Lead and cadmium concentration was determined in serum of 30 malignant and 20 controls and tissue concentration was assessed in 30 malignant breast tumor patients. Two samples from each patient were taken during lumpectomy or mastectomy procedure. 5 ml blood sample was taken after 12 hours of fasting from cubital vein and 2 ml serum was separated after centrifugation. Our results showed highly significant difference in both serum (Pb- t=3.2, p<0.001, Cd- t=7.4, p<0.001) as well as tissue (Pb- t=10.8, p<0.001, Cd- t=11.6, p<0.001) lead and cadmium in malignant breast tumor patients as compared to controls. Thus we conclude that lead and cadmium have possible detrimental role in causation of breast cancer and can be a potent diagnostic marker of the disease process.

INTRODUCTION

According to WHO, Breast cancer accounts for 22% of cancer among females worldwide and 16% of all types of cancer deaths globally.[1,2] Although the incidence of Breast Cancer increases with age, certain life style and environmental factors play an important role on Breast Cancer risk[3,4]. In India Breast Cancer is the most common cancer among women in many regions and has overtaken cervix cancer. [5] Presently the percentage of Breast Cancer among male population has risen above 2% of all cancer.[6,7] The role of metals in the development and inhibition of cancer has a complex character. In the past decades some metals including cadmium and lead has been recognized as human and animal carcinogenesis in addition to primary carcinogens.[8,9,10] Heavy metals as environmental pollutants, have been implicated in human carcinogenesis by various researchers.[11,12] The aim of this study is to evaluate the role and effects of lead and cadmium in the development of Breast Cancer.

MATERIAL AND METHODS

The present study was conducted in the department of Surgery, Ajmal Khan Tibbiya College and the Department of Pharmacology J.N. Medical College A.M.U., Aligarh, India on 30 malignant breast tumor patients aged 15-165 yrs of age and 20 controls.

A detailed medical history and a thorough systemic examination with routine haemogram, urine for routine and microscopic examination, random blood sugar and X-ray chest were performed. Mastectomy/ lumpectomy was done under general anesthesia/local anesthesia and about l gm of disease breast tissue was dissected and dissolved in 4ml of acid (3ml nitric acid + 2ml perchloric acid) in a compressed vial, after trimming of fat and stored until analyzed. 5 ml blood sample was taken by venepuncture from the cubital vein after 12 hours of fasting in sterile syringe and 2 ml serum was separated by clotting and centrifuging it at 2000 rpm for 10 min and stored at 4°C until analyzed. The normal tissue (taken from the same breast of the same patient, 2cm away from the tumor), serum and disease tissue were analyzed for heavy metals lead and cadmium by Atomic absorption spectro-photometer (4139 ECIL). The statistical analysis was done by applying student 't' test.

RESULTS

The age of the patients ranged from 15-65 years, with the mean age of 43.8 ± 12.7 yrs (Table no.1). There were 28 females

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(93.3%) and 02 males (6.7%) in our study, with female: male ration of 14:1 (Table 2).

Table No. 1 Distribution of Malignant breast tumor case and controls according to age

Range (in years)	Malignant Breast Tumor		Controls	
	Number	Percentage	Number	Percentage
15-25	2	6.67	10	50
25-35	4	13.33	10	50
35-45	11	36.67		
45-55	9	30.0		
55-65	3	10.0		
65-75	1	3.33		
Total	30	100	20	100
Mean ± SD	43.87 ± 12.66		29.35 ± 5.7	

Table No. 2 Distribution of Malignant breast tumor case and controls according to sex.

Sex	Malignant Breast Tumor		Controls	
	Number	Percentage	Number	Percentage
Male	02	6.7	10	50.0
Female	28	93.3	10	50.0
Total	30	100	20	100

There was a significant difference between the age of malignant breast tumor and controls (t=6.2, p<0.001).

50% patients used running tap water, 35% used hand pump water and only 15% took water from other sources in case of malignant breast tumor group. (Table no. 3).

Table No. 3 Source of water

Source of Water	Malignant breast tumor	Controls
Running top water	50%	80%
Hand pump water	35%	15%
Other sources	15%	5%

Only 30% patients were residing around the industrial area (Table 4).

Table No. 4 Factory in the surrounding

Factory	Malignant breast tumor	Controls
Present	30%	5%
Not Present	70%	95%

Serum cadmium levels in malignant breast tumor group ranged from 0.46 to 2.25 ug/l (mean 1.22 ± 0.5) and in controls the range was found to be 0.24 to 0.82 (mean 0.4 ± 0.2) (Table-5) and tissue cadmium levels varied from 2.77 to 9.44ug/g (mean6.48 ± 1.89) (Table-6).

Table No. 5 Serum Cadmium Levels in ug/L, in malignant breast tumor and controls

Serum Cadmium Level (ug/l)	Malignant Breast Tumor		Controls	
	No. of Cases	Percentage	No. of Cases	Percentage
0.0-0.50	01	3.33	13	65.0
051-1.0	14	46.67	7	35.0
1.01-1.5	7	23.33		
1.51-2.0	08	26.67		
Total	30	100	20	100
Mean ± SD	1.22 ± 0.5		0.4 ± 0.2	

There was a significant difference between serum cadmium levels of malignant group and controls (t- 7.4, p<0.001).

Table No. 6 Tissue Cadmium Levels in ug/g, in malignant breast tumor

Tissue Cadmium Level (ug/g)	Malignant breast tumor			
	Tumor tissue		Normal tissue	
	No. of cases	Percentage	No. of cases	Percentage
0-20.0	-	-	20	66.7
2.01-4.0	03	10.0	07	23.3
4.01-6.0	13	43.3	03	10.0
6.01-8.0	5	16.7		
8.01-10.0 above	9	30.0		
Total	30	100	30	100
Mean ± SD	6.48 ±1.89		1.58 ±1.10	

A significant difference was found between serum & tissue levels of malignant tumor (t=14.6, p<0.001) & also between normal and diseased tissue of malignant breast tumor group (t=12.2, p<0.001).

Serum lead levels of malignant breast tumor group varied from 1.83 to 9.98 ug/l (mean 4.83 ± 2.5) and in controls the range was 1.18 to 9.21 (mean 2.8 ± 1.7ug/l) (Table 7). There was a significant difference between serum lead levels of malignant group and controls (t-3.2, p<o.001). Tissue lead levels in malignant breast tumor group ranged from 8.04 to 16.5 ug/g (mean 11.80 ± 2.58). (Table -8).

Table No. 7 Serum lead Levels in ug/L, in malignant breast tumor and controls

Serum lead level (ug/l)	Malignant Breast Tumor		Controls	
	No. of Cases	Percentage	No. of Cases	Percentage
0.0-1.5	-	-	2	10.0
1.51-2.5	5	16.67	10	50.0
2.51-3.5	7	23.33	3	15.0
3.51-4.5	7	23.33	2	10.0
4.51-5.5 above	11	36.67	3	15.0
Total	30	100	20	100
Mean ± SD	**4.83±2.5**		**2.8±1.7**	

Table No. 8 Tissues lead levels in ug/L, in malignant breast tumor

Tissues lead level (ug/g)	Malignant Braest Tumor Controls			
	Tumor tissue Percentage		Normal Tissue	
	No. of cases	Percentage	No. of Cases	Percentage
0-4	-	-	16	53.3
4.01-8	4	13.33	8	26.7
8.01-12	14	46.7	6	20
12.01-16	10	33.3	-	-
16.01-20.0	2	6.7	-	-
Total	30	100	30	100
Mean ± SD	11.80 ±2.6		4.42±2.8	

A significant difference was noted between serum and tissue levels of malignant breast tumor group (t=10.2, p<0.001) and also between normal tumor group (t=10.8, p<0.001). Maximum number of patients in malignant breast tumor group were in the range of 8.01– 12ug/g (14 out of 30 patients).

DISCUSSION

Lead and cadmium are known carcinogens and we have tried to establish the fact that heavy metals are closely related to the development of breast cancer. Previous studies have also stated that a close association exists between heavy metals like lead and cadmium and breast cancer development.[11, 12] Researchers even suggests that exposure to cadmium had significant risk of

developing ovarian as well as renal cancer.[13] Singh *et al* have concluded the presence of high concentration of heavy metals in gall bladder cancer patients, indicating a possible role of heavy metals in gall bladder carcinogenesis.[14]

In our study, out of 30 malignant breast tumor patients, twenty eight (93.3%) were females and two were males (6.7%), a finding concordant with the study of Hussain *et al*, which reported 4% incidence of breast cancer in males[7]. Another study done in England and Wales showed that the incidence of female breast cancer has risen in the recent decade with increase in male breast cancer.[15] In Egypt National cancer institute reported the incidence of breast cancer among males was 2.2% & in females it was 35.1% in a series of 10,556 patients.[16] Male breast cancer constitutes <0.1% of incidence.[17]

The age of malignant breast patient ranged from 15-65 yrs of age (mean 43.8± 12.66 yrs). There was a significant difference between the age of malignant breast tumor group and controls (t=6.2, p<0.001) Breast cancer frequency has been found to be 20% among women <40 yrs old in Turkey where as it was around 5% in Western Europe and in United states of America. Patients who have ≥ 50 yrs of age were more likely to have increased risk of breast cancer. The incidence of breast cancer increases with age, doubling about every 10 yrs.[18] Mc pherson and Vogel *et al* suggest that the risk of breast cancer increases among older women (≧ 50 yrs of age).[19, 20] MC Elroy *et al* had carried out an age related study and found mere risk of breast cancer in younger age.[21] Although study done by Julin *et al* showed increase incidence of breast cancer in post menopausal women.[22] A hospital based nested case control study done in Turkey suggests that the patients with age ≥ 50 yrs had high risk for the development of Breast Cancer.[19, 20] Hussain *et al* found peak incidence of breast cancer between the age group of 41-50 yrs of age.[7] A study done by Mona -El-Harouny *et al* showed that the mean age for the breast cancer in Egypt was 51 ± 9.34 yrs and in European females it was 61.6 ± 11.8 yrs while Elattar *et al* shows median age for breast cancer was 48 yrs in Egypt.[23, 24, 25, 16]

A Large no. of epidemiologic studies associate potential risk factors for cancer with metals which are naturally found in the environment. Human exposure to these metals may result from air, drinking water or food.[26,27] Various studies conducted all over the world to investigate the role of environmental pollutants in the etiology of cancer. In a Chinese study, long term exposure to lead and cadmium shows higher incidence of gastrointestinal and lung cancer.[28] Another study of Egypt concluded causal association between high levels of cadmium with breast and Pancreatic Cancer.[23, 29] A case control study in Pennsylvania to investigate the role of environmental pollutants in lung cancer etiology showed that the residents close zinc smelters and steel manufacturing plant had double risk of lung cancer due to polluted soil by arsenic and cadmium.[30] A Belgian study also showed similar results and mentioned that participants who resided near zinc smelter had four fold high risk of lung cancer.[31] A North Indian epidemiological study carried out by out Thakur *et al* to estimate the level of cadmium, chromium, selenium and mercury in drinking water of the rural agricultural community found high concentration of these heavy metals in drinking water.[32]

The present study revealed that the mean serum (8.92 ± 4.52) and tissue cadmium levels (6.48 ± 1.89) were significantly higher than controls (0.4 ±0.2 t=7.4 p<0.001) and normal tissue (1.58 ± 1.10) (t= 14.6, p<0.001). Cadmium concentration in urine samples was also analyzed and significantly higher Cadmium concentration was found in breast cancer patients as compared to benign breast disease.[21, 23, 25] In an Egyptian study, average tissue cadmium concentration was significantly higher in patients with breast cancer than that of benign breast disease.[25] Another study done by Ionescu which is in consonance with the present study showed significantly higher cadmium concentration in cancer biopsies as compared to healthy control group.[33] Other subsequent studies were in accordance with the present study, Strumylaite *et al* revealed statistically significant difference in cadmium concentration in Malignant breast tumor as compared to be benign group.[34] Morgan *et al* estimated cadmium concentration in renal and hepatic tissues and blood of bronchogenic carcinoma patients revealed significant increase in cadmium levels.[35] Walkes *et al* found high cadmium concentration in proliferative prostate lesion.[36]

Another study which is consonance with the present study was done by Singh M *et al*, they estimated levels of heavy metals in gall bladder carcinoma patients and found high levels of cadmium and they concluded that heavy metals are in higher concentration in carcinoma gall bladder indicating possible role of heavy metals in gall bladder carcinogenesis.[14] Farid Saleh *et al* investigated the blood level of cadmium in 50 Breast cancer patients and reported significantly higher cadmium level in carcinoma patients as compared to controls and stated that high cadmium levels were significantly associated with micronucleus formation in lymphocytes.[5] Strumylaite underwent a study on 57 breast cancer patients and 51 patients with benign breast disease, they estimated cadmium concentration in biological media including diseased biopsy, healthy tissue, urine and blood of each patient and mentioned that average cadmium concentration was significantly higher in malignant tumor patients than that of benign with no significant difference is healthy tissues between both the groups.[25] Abo El Atta *et al* underwent an in vitro study using normal cultured mammary cells and breast cancer cells to find out the possible mechanism for cadmium induced breast cancer. They reported that cadmium chloride is cytotoxic to 1^{o} cultured cells and induced DNA damage in both mammary cultured cells and breast cancer cells due to mutations in their nucleotides sequence.

They advocated that cadmium could be considered as a chemical carcinogen that may act either as initiator or promoter to mammary cancer. [37] Mc Elroy carved out population based case control study on 246 women with breast cancer to estimate the cadmium concentration in urine samples and found statistically significant two folds increase in breast cancer risk for women having higher cadmium concentration.[21] Eliane Kellen *et al* conducted a study to assess the relationship between exposure to cadmium and bladder cancer risk and suggested that individuals with increased exposure to cadmium

had high risk for bladder cancer.[38] Phillip and Hughes studied the residents of Shipham village, Somerset, England, who were exposed to high soil levels of cadmium and demonstrated a small but statistically significant risk for ovarian cancer in the cadmium exposed population.[39] In an Egyptian study, serum cadmium levels were assessed in 31 newly diagnosed cancer patients and high levels in pancreatic cancer patients was found as compared to controls.[29] In a Belgian study, authors recruited participants who resided close to zinc smelters and control group with less exposure to assess association between environmental cadmium exposure and caner they reported fourfold lung cancer cases among high exposed population.[31] A study done by Antila concluded that the mean cadmium concentration in 43 cancer patients did not differ significantly from 32 healthy controls this study is contradictory with the present study.[40]

In the current study the mean lead levels in serum (4.83+2.5) and tissue (11.8+2.6) were significantly higher as in serum (t=3.2, peo.001) and in tissue (t=10.8, p <0.001) in malignant breast tumor group as compared to control group (2.8±1.7) and normal tissue group (4.4 ± 2.7). A finding discordant with Mona-El-Harmony who showed, that there was no significant difference in lead levels between cancerous and non- cancerous group.[23] High levels of lead were found in blood and head hair samples of breast cancer.[41] An Iranian study showed no significant difference between metal concentration in different parts of breast cancer tissues.[42] In a Chinese study, Wang *et al* investigated the probable association between long term environmental exposure to lead and cadmium and cancer incidence, they found higher incidence of Gastro–intestinal and lung cancer among population exposed to contaminated river.[28]

Although in an Egyptian study authors found no significant difference between cancerous and non cancerous group but this finding is discordant with the finding of Ionescu who demonstrated a significant increase in lead and zinc concentration of breast cancer patients. [23, 33] Siddiqui *et al* assessed the association between environmental exposure to lead and risk of breast cancer in 250 malignant breast tumor patients to determine the potential of changes in trace elements concentration as a diagnostic marker or its etiological involvement in the disease. Blood lead was significantly higher in malignant cases than those of controls (p<0.005). Lead levels were also higher in tumor tissue as compared to their respective normal tumor free breast tissues though non-significant.[43] Edgar Drake & Sky Peck reported low levels of lead in lung tumor as compared to normal tissues with no significant difference between the two.[11]

Mulay *et al* also showed low level of lead in malignant tissues than normal tissue.[44] Roy *et al* conducted the study to assess cadmium induced DNA damage in different mammary cell lines and stated that cadmium can induce DNA damage and this damage may be due to inability of cadmium to increase reactive oxygen species resulting in lipid per oxidation, DNA damage and altered gene expression or due to in activation of the enzymes responsible for DNA repair by displacing essential metals, this study is in consonance with the study of Mona El-Harouny *et al* who showed significant DNA damage.[45, 23]

Ellen K *et al* reported the carcinogenic activity of lead and suggested that its vole in carcinogenesis was permissive rather than causative that is, lead can increase the risk of cancer by reducing the ability of the cell to protect or repair DNA damage by other exposure rather than by causing alterations in DNA directly.[46] Higher levels of cadmium, lead and mercury were also reported by Iman Al Saleh and shinwari in brain tumor patients.[47]J Palus *et al* in their study assessed the genotoxic damage in somatic cell workers in a polish battery plant after high level occupational exposure to lead and cadmium and concluded that lead and cadmium induced clastogenic as well as aneugenic effects in peripheral lymphocytes, indicating a potential health risk for working population with significant exposure to these heavy metals.[48] Hengstler *et al* studied DNA single strand, DNA- SSB induction and repair capacity for 8-oxoguanine in mononuclear blood cells of 78 individuals co-exposed to cadmium, cobalt and lead. Exposure to these heavy metals was determined in air blood and urine. They concluded multiplicative effects for co-exposure of cadmium, cobalt and lead and quoted that co-exposure may cause genotoxic effect.[49]

Arinola O.G *et al* estimated cadmium lead and other elements in the serum of breast cancer patients with healthy controls and concluded no significant difference in breast cancer patients compared with the healthy control.[50]

CONCLUSION

We estimated the levels of heavy metals (lead and cadmium) in serum diseased tissue and normal tissue of malignant breast tumor patients and healthy volunteers and found marked variation in the levels of these elements in diseased state as compared to healthy controls. Thus we conclude that these metals have detrimental role in the development of breast tumor. To establish the fact, a detailed study on larger sample size is needed.

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