Environmental Exposure to Lead and Breast Cancer: Is there any Association?

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ABSTRACT

Breast cancer is the most common malignancy among females affecting approximately one out of ten women. Experimental occupational studies suggest a potential role of lead in the etiology of human cancer. Lead is a ubiquitous toxic contaminant of our environment that poses a substantial threat to human health. Ten newly diagnosed breast cancer patients from King George's Medical University, Lucknow, India, who had not undergone any previous treatment for their tumors and Ten healthy women as control were chosen for the study. Blood from the study group collected at the time of lumpectomy / mastectomy. Blood lead was determined using Graphite furnace atomic absorption Spectrometer. The mean blood lead level was found significantly higher in subjects having cancer (19.75 ± 10.99) as compare to control group (not having cancer) (6.63 ± 0.9) (p<0.01). There were significant negative correlations of blood lead with blood GSH level (r = -0.64, p<0.05) and Blood δ-ALAD activity (r = -0.74, p<0.05). Blood lead had significant positive correlations with blood MDA level (r = 0.67, p<0.05). On the basis of these observations lead levels and oxidative stress were found significantly higher in the subjects having breast cancer which likely to show that lead-induced oxidative stress as one of the mechanism associated with the genesis of breast cancer in women. However, results of this study may be limited due to limited sample size and needs to be studied with larger population.

Keywords: Breast cancer, Delta-Aminolevulinic Acid Dehydratase (δ-ALAD), Reduced Glutathione (GSH), Malondialdehyde (MDA).

1. INTRODUCTION

Breast Carcinoma is one of the most common neoplasm in women (Ana-Maria & Dietrich 2011) and is a leading cause of cancer related deaths worldwide. Over 100, 000 new breast cancer patients are estimated to be diagnosed annually in India (Agarwal et al., 2007). The risk factors associated with breast cancer may exert their effects via generation of reactive oxygen species (ROS), which are recognized to induce oxidative DNA damage and neoplastic transformation.

Reactive oxygen species are being increasingly implicated in breast cancer development (Yeh et al., 2005). The endogenous amount of reactive oxygen species may be enhanced by the exposure to genotoxic metals. Metals are accumulated in compartments of the body. They interfere with many cellular reactions. Excretion may take years or decades (Elinder et al., 1994; Hayes, 1997). The four most predominant mechanisms for metal carcinogenicity include (1) interference with cellular redox regulation and induction of oxidative stress, (2) inhibition of major DNA repair, (3) deregulation of cell proliferation, and (4) epigenetic inactivation of genes by DNA hypermethylation (Mulware, 2013). The carcinogenic potential of cadmium, nickel, and chromium compounds is well established for humans and experimental animals (IARC, 1990; IARC, 1993). Regarding lead, the epidemiological data are not conclusive with respect to human carcinogenicity, but carcinogenic and cocarcinogenic effects of lead compounds have been demonstrated in experimental animals (Cohen et al., 1996).

2. MATERIALS AND METHODS

Ten newly diagnosed breast cancer patients from King George's Medical University, Lucknow, India, who had not undergone any previous treatment for their tumors, were chosen for the study. Informed consent was obtained from all the participants. Blood samples were obtained by venous arm puncture in heparinized tubes.

Blood lead was determined using an atomic absorption spectrometer equipped with graphite tube atomizer (GTA) (Varian SpectrAA 250+, Varian Australia Pty Ltd., Victoria, Australia) (Khullar, 1999) . Blood lead level was expressed as μg/dL.

3. STATISTICAL ANALYSIS

The significance of differences between mean values of the physical parameters in the study and control groups was compared using Student's t-test after confirming the homogeneity of variance between the two groups (Table 1). For discrete variables Chi-square test was applied to see the statistical significance. Student's t-test was used to compare the mean values of the lead level in the blood study and control group. Linear regression analysis was performed to determine the relationship between lead and MDA, GSH & (δ-ALAD).

4. RESULTS

The demographic data of the subjects in malignant and disease free control groups collected from KGMU, Lucknow are presented in Table1. Women in the both groups were closely matched for age. Seventy percent (70%) cases in control group and 80% cases in the malignant group were drawn from urban areas in and around Lucknow.

Table 2 represents the levels of lead in the blood of control and malignant group. The mean blood lead level was significantly higher ($p<0.01$) in malignant group (19.75 ± 10.99) as compare to control group (6.63 ± 0.9). The blood δ-ALAD activity was significantly lower ($p< 0.001$) in study group when compared with the control group. Blood MDA levels were significantly higher ($p< 0.05$) while GSH contents were significantly lower ($p< 0.001$) in study group as compared to control group. Figures (1-3) represent the strength of relationships between blood lead and oxidative stress markers. There were significant negative correlations of blood lead with blood GSH level ($r = -0.64$, $p<0.05$) and Blood δ-ALAD activity ($r = -0.74$, $p<0.05$). Blood lead had significant positive correlations with blood MDA level ($r = 0.67$, $p<0.05$).

5. TABLES

Table.1 Characteristic of the subjects

Parameters		Cases (n=10)	Control (n=10)
Age (Yrs)		47.63 ± 8.16[#]	47.90±9.48
Age at menarche(yrs)		12.81±0.98	12.81±0.87
Age of menopause(yrs)		44.14±3.71	44.33±3.01
Age at first birth		24.5±5.66	23.42±3.04
Number of children		2.18±2.31	2.09±1.97
Breast feed (months)		10.36±8.52	12.±11.06
Abode	Urban	7	8
	Rural	3	2
Menstrual status	Pre	1	1
	Peri	2	3
	Post	7	6
Clinical stage	Stage II T2 N1 M0	4	NA
	Stage III T3 N1 M0	5	NA
	Stage IV T4 N2 M0	1	NA
Side of lump	Left	6	NA
	Right	4	NA
Diet	Veg	7	7
	Non-veg	3	3

[#]Values present in mean±SD

****p< 0.05***

Table.2 Level of lead in the blood from women with cancer as compared with disease free controls

Metals	Control group Mean ± SD n=10	Malignant group Mean ± SD n=10	p-value
Pb	6.63 ± 0.9	19.75 ± 10.99	p<0.01

Pb: µg/dL,

Table. 3 Oxidative stress parameters in blood of the women with malignant breast lesions

Parameters	Control group (n=10) Mean±SD	Study group (n=10) Mean±SD	p-value
δ-ALAD	4.49±1.02	2.25±1.20	< 0.001
MDA	11.18±2.58	18.30±9.87	< 0.05
GSH	23.53±4.65	7.89±5.55	< 0.001

* ***p<0.05, significantly different from the control group***

δ-ALAD: µmol PBG formed/min/L blood, MDA: nmol/ml blood, GSH:µmol/ml blood,

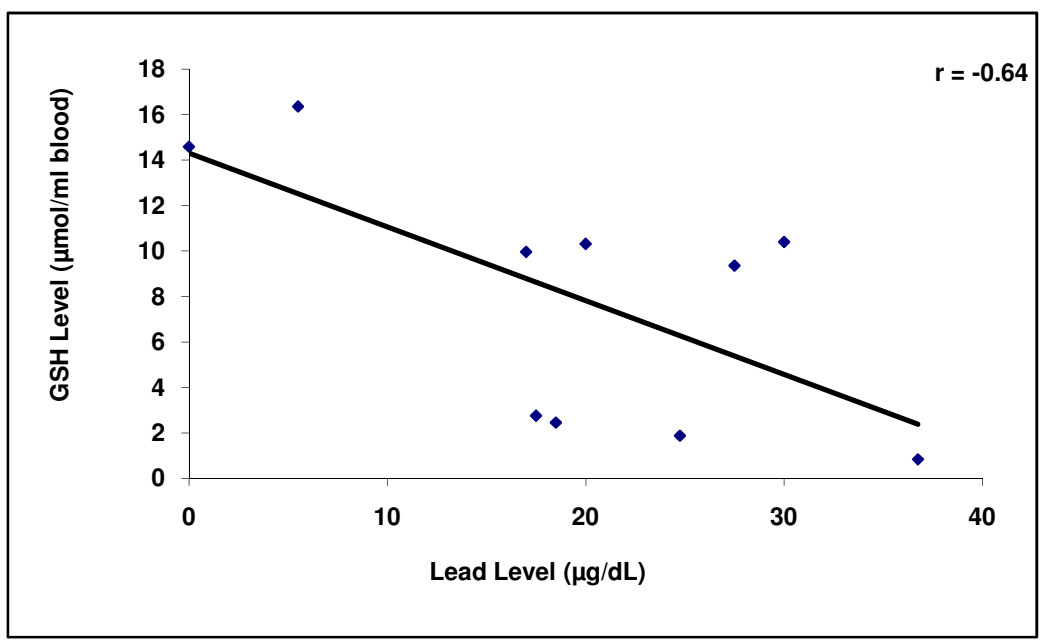

Figure1: Blood lead levels plotted against GSH level in breast cancer cases indicating the condition of oxidative stress

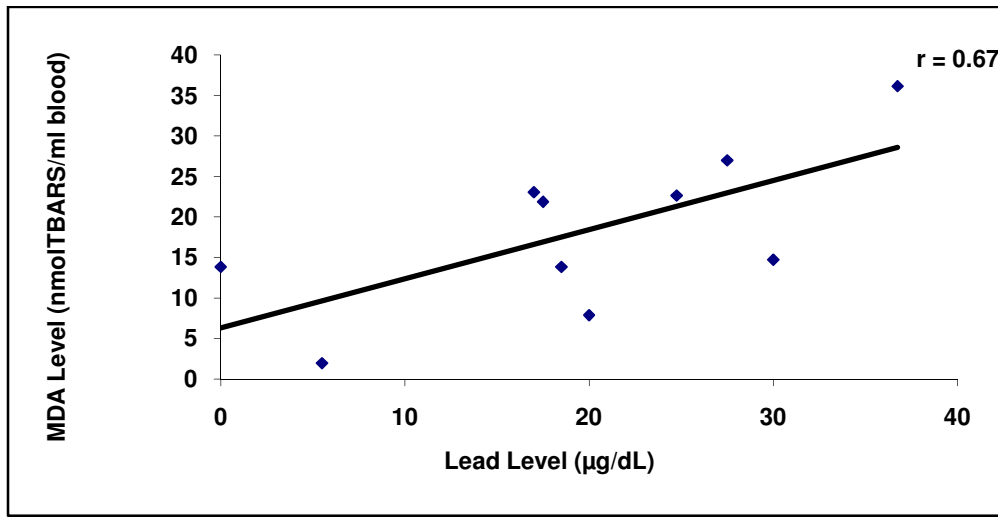

Figure2: Blood MDA level plotted against blood lead levels

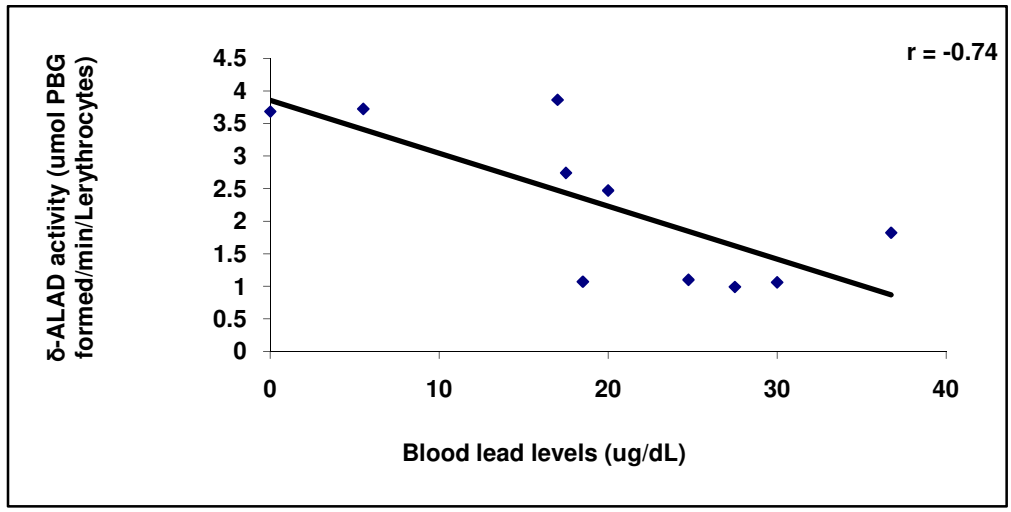

Figure3: Blood δ-ALAD activity plotted as a function of blood lead levels

6. DISCUSSION & CONCLUSION

Recent studies have reported the lead's potential for inducing oxidative stress and evidence is accumulating in support of the role for oxidative stress in pathophysiology of lead exposure. Damage to the breast epithelium by oxygen free radicals can lead to fibroblast proliferation, epithelial hyperplasia, cellular atypia and breast cancer.

Studies have shown increased lipid peroxidation in solid tumors and malignant cell lines including breast tumors (Kumaraguruparan et al., 2002). The results of the present study are also consistent

with these previous findings. Huang et al. (1999) demonstrated that there was significantly increased lipid peroxidation in the serum of breast cancer patients. In the present study also, in agreement with the previous studies MDA level was found significantly higher while GSH level was significantly lower in study group as compared to control. We propose that lead could enhance lipid peroxidation in the study group, through the promotion of membrane physical changes, which would favor the propagation of oxidative stress. Blood levels of malondialdehyde, a product of lipid peroxidation were strongly correlated with blood lead concentrations in lead exposed workers (Jiun and Hsien, 1994).In the present study, a three times higher blood lead level in women with breast cancer than in controls (Table 1) might be expected to generate ROS leading to lipid peroxidation as statistically significant higher levels of malondialdehyde in study group as observed in the present study.

Accordingly, GSH plays a vital role in the protection of cells against oxidative stress .Ercal et al. (1996) observed increased oxidative damage in lead-exposed cells by means of a decreased GSH/GSSG ratio and increased MDA levels. In the present study we found elevated blood lead with decreased glutathione in the blood of the subjects having malignant breast lesions. It shows the negative correlation between blood lead and glutathione level.The lower GSH levels seen in breast cancer patients support the hypothesis that the glutathione status is inversely related to malignant transformation. ALAD is also the most known enzyme that is inhibited by lead via direct binding of lead to the SH groups that are essential for the catalytic acitivity of the enzyme (Bernard and Lauweys, 1987). Several studies have been reported showing how accumulated ALA induces ROS generation (Monteiro et al., 1991; Hermes-Lima, 1995). The evidences for ALA-induced oxidative stress were also reviewed by Bechara (1996). Recently, Sakai and Morita (1996) found that threshold value of blood lead for δ-ALAD inhibition was extremely low (approximately 5 μg/dL). Inhibition of δ-ALAD by lead accounts for the accumulation of δ-ALA in blood and urine; urinary δ-ALA has also been used as a biomarker for lead exposure or a marker of early biologic effect of lead (Klaassen, 1996). In the Present study a negative correlation was observed between blood Pb and δ-ALAD levels among the subjects with breast cancer. In the present study, Pb showed statistically significant negative correlation with δ-ALAD in the subjects with breast cancer.

On the basis of above observations lead levels and oxidative stress were found significantly higher in the subjects having breast cancer which likely to show that lead-induced oxidative stress as one of the mechanism associated with the genesis of breast cancer in women. However, results of the present study may be limited due to limited sample size and inability to other potential confounding effects need to studied further with larger population.

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