Journal of Clinical Toxicology
ISSN: 2161-0495
El-Harouny et al. J Clinic Toxicol 2011, 1:2
DOI: 10.4172/2161-0495.1000109
Research Article Open Access

Chronic Toxicity of Some Heavy Metals and Breast Cancer in Egyptian Females

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Abstract

Heavy metals as environmental pollutants have been recognized to have a role in induction of malignant human growths. Recently, certain heavy metals showed a close association to breast cancer. This research was conducted to find out the role of some toxic heavy metals (cadmium, iron, copper, lead and zinc) in induction of breast cancer in-vivo. The study was carried out on 100 female patients: 75 with breast cancer (cancerous group) and 25 with benign breast diseases (non-cancerous group). Patients were chosen from those attending to the Oncology Center, Mansoura University. Heavy metals concentrations were measured in the urine and breast tissue samples using inductive coupled plasma (ICP) - spectrometer. The present results showed a significant increase in urine and tissue cadmium concentrations and urine copper concentration in cancerous patients compared to their corresponding non-cancerous ones ($p < 0.05$). Also, there was a significant reduction in iron concentration in urine samples of cancerous group compared to their corresponding non-cancerous one ($p < 0.05$). On the other hand, lead had no significant difference between cancerous and non cancerous groups but it was generally high in the tissue samples while zinc had no significant difference between studied groups. It could be concluded that the present study posits a causal association between cadmium and copper increase with reduction of iron and breast cancer.

Keywords: Cadmium; Copper; Iron; Zinc; Lead; Breast Cancer; Egyptian

Introduction

Heavy metals carcinogenesis is a process driven by their reaction with critical molecules in body cells to cause cancer [1]. The role of metals in the development and inhibition of cancer raised many questions about their essential and toxic effects on human health [2]. In the past 25 years, certain heavy metals as cadmium, nickel, arsenic, beryllium and chromium VI have been recognized as human or animal carcinogens as declared by the International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP) [3].

Chronic exposures to various heavy metals are nearly unavoidable in daily life, such as from airborne particles, soil, water and subsequently food [4]. Recently, industrial applications, drug formulation, food additives, manufacturing of semiconductors, mining, smelting, refining metal ores, cement-manufacturing plants, electroplating facilities, gasoline and diesel vehicles and particles resulting from tire wear lead to release of the different heavy metals in the environment [3].

In Egypt, closed Manzallah Lake is seriously contaminated with heavy metals including cadmium, as a result of increasing discharge of untreated industrial wastes as well as agricultural irrigation by wastewater [5]. Hassanien [6] assessed human health risk estimates in residents from different regions in Cairo, Egypt. He concluded that, the current levels of copper, chromium, cadmium, lead, manganese, vanadium, arsenic, nickel, antimony and titanium were higher than those considered safe for the general population.

Worldwide, breast cancer is the most common malignancy that affects women [7]. In Egypt, the incidence attained about 37.5% of total cancer cases among Egyptian females and is considered the fourth cause of death [8]. Over the past decades, there has been a significant continuous increase in breast cancer rates. Yet, the underlying causes of this increase are still largely unknown [9].

Vahter [10] mentioned that there was a lack of information on whether environmental – related health effects including carcinogenesis were more prevalent in women. The present study is designed to find out the role of some toxic heavy metals (cadmium, iron, copper, lead and zinc) in induction of breast cancer *in-vivo*.

Materials and Methods

This study was carried out on 100 female patients attending to the Oncology Center, Mansoura University, Dakahlia Governorate, Egypt during the period from December 2008 till December 2009. Their ages ranged from 30 -70 years. Relevant information was obtained from each patient before surgery regarding residence, occupational history, smoking habits and reproductive history. Patients with positive family history of breast cancer were excluded from the study. Informed consent was obtained from each patient.

Study groups

Patients were divided into two groups. A cancerous group (75 female patients) with histologically confirmed breast cancer lesions. A non-cancerous group (25 female patients) with non risky non proliferative benign breast diseases that served as a control group.

Study design

According to Ionescu [11], 10 ml urine sample and 10 gm of breast adipose tissue were obtained from each patient. Samples were

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Received October 01, 2011; **Accepted** November 14, 2011; **Published** November 16, 2011

Citation: El-Harouny MA, El-Morsi DA, Ahmed BRA, El-Atta HMA (2011) Chronic Toxicity of Some Heavy Metals and Breast Cancer in Egyptian Females. J Clinic Toxicol 1:109. doi:10.4172/2161-0495.1000109

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kept in polyethylene containers that were cleaned using multistep acid leaching and frozen immediately at -20°C until analysis. Digestion of samples was done using advanced microwave digestion system "Milestone ETHOS-1 lab station with easy-WAVE/easy-CONTROL HPR1000/105 high pressure segmented rotor". The concentrations of cadmium (Cd), iron (Fe), copper (Co), lead (Pb) and zinc (Zn) in both urine and tissue samples were quantified using ICP-spectrometer (iCAP 6000 Series; Thermo Scientific) according to manufacturer instructions. The standards for calibration of the following heavy metals (Cd, Fe, Co, Pb and Zn) were purchased from Sichuan Xinju Mineral Resource Development Stock Co., Ltd

Statistical analysis

Data were analyzed using SPSS version 16 and represented as median and interquartile range (IQR). Mann-Whitney test and Wilcoxon Signed Ranks test were performed to study the correlation between variables. Significance was set at $p < 0.05$. Odds ratios and corresponding 95% confidence interval (CI) were calculated to estimate the magnitude of association between independent variables.

Results

The average ages for patients with benign breast tumor are 40.4±11.43, while average age for patients with breast cancer tumor is 51± 9.43.

The demographic and reproductive data of patients shows that the rural residents, married with high parity and postmenopausal females have a higher risk for developing breast cancer in which: the percentage of cancerous patients who inhabited in rural areas is 69.3% versus 30.7% who inhabited in urban areas. The majority of cancerous patients (97.3%) are married and 2.7% are single with 95% confidence interval (1.26 – 18.11) for females having three or more children. Postmenopausal cancerous patients represented 57.3% versus 42.7% are premenopausal. Statistical analysis of the menopausal age shows that: in cancerous patients, about 6.7% are less than 45 years old, 38.7% are between 45 – 49 years old, while 12% are between 50 – 54 years old at menopause (Table 1).

Significant increase in cadmium concentrations were detected in urine and tissue samples of cancerous patients compared to their corresponding non-cancerous one. On the other hand significant increase in copper concentration is observed in urine samples compared to their corresponding non-cancerous group ($p < 0.05$). Iron concentration is found to be significantly reduced in urine samples of cancerous patients compared to their corresponding control group ($p < 0.05$). Lead has no significant difference between cancerous and non cancerous group but it is generally high in the tissue samples while zinc has no significant difference between studied groups (Table 2).

Figure 1 demonstrates that 56% are housewives; 24% are farmers; 16% are factory workers; while 4% are teachers.

Discussion

In the present study, the concentrations of six heavy metals (cadmium, copper, iron, lead and zinc) were estimated in the urine and tissue samples of patients with breast cancer; based on previous studies that possessed a close association between heavy metals and development of breast cancer. The average age of the Egyptian female patients with breast cancer described in this study was 51± 9.43 years. While the mean age for breast cancer in European females is more common in older ages (61.16 ± 11.8 years) [12,13]. Another study done at the Egyptian National Cancer Institute by Elattar [8] found that the median range for breast cancer is 48 years old.

In the current study, the mean urinary cadmium concentration in patients with breast cancer was significantly higher than that of patients with benign breast diseases. The present findings supported the work of McElory [14], who observed significant two folds increase in breast cancer risk in women having higher urinary cadmium concentration.

Similar findings were reported by Strumylaite [13] who detected significant higher urinary cadmium concentration in 57 patients with breast cancer compared to 51 patients with benign breast diseases.

The increased urinary cadmium concentration is an indicator for total body burden of the metal, indicating long life exposure with increased risk of developing breast cancer.

Data of the present study revealed that the average tissue cadmium concentration is significantly higher in patients with breast cancer than that of patients with benign breast diseases. This is contradicted with the study done by Antila [15] who concluded that the mean cadmium concentration in 43 cancer patients did not differ significantly from 32 healthy control; although cadmium content reached a high concentrations in both groups. They accounted the high concentrations of cadmium to the characteristic feature of cadmium being tightly bound to adipose tissue and poorly excreted in milk.

Other subsequent studies were in accordance with the results of the present study. Ionescu [11] performed an analysis for cadmium in 20 frozen breast cancer biopsies and found that the average cadmium concentration was significantly higher in cancer biopsies than healthy control group. Strumylaite [16] who assessed cadmium concentration in breast tissue samples of patients with breast cancer (n=21) versus those with benign breast diseases (n=19) and revealed a statistically significant increase in cadmium concentration in malignant breast tissues compared to their corresponding benign group.

Strumylaite [13] underwent a study on 57 breast cancer patients and 51 patients with benign diseases and mentioned that the average cadmium concentration in malignant tumors was significantly higher than that of benign tissues with no significant difference in healthy tissues between both groups. The mentioned authors attributed the non – significant findings of cadmium concentration in breast cancer of Antila [15] to the site of sampling. They proposed that cadmium analysis may be done in the tissue near to the malignant tissue but not in the malignant tissue itself.

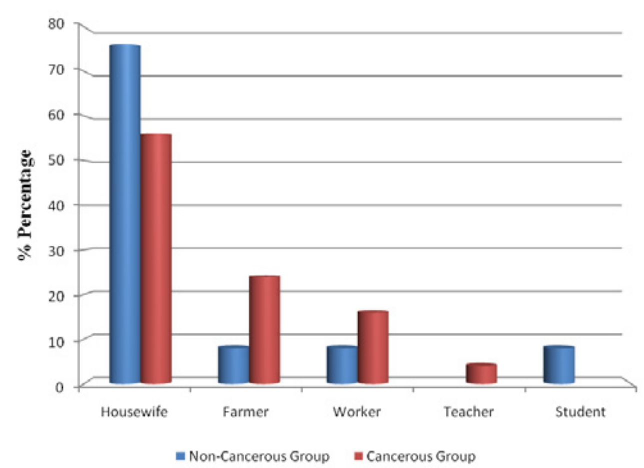

Figure 1: Percentages of occupations in both cancerous and non-cancerous groups.

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A study was done by Abo El - Atta [17] to find out the possible mechanism for cadmium induced breast cancer. They underwent an in vitro study using normal cultured mammary cells and breast cancer cells and reported that cadmium chloride is cytotoxic to primary cultured cells and induced DNA damage in both mammary cultured cells and breast cancer cells due to the mutations in their nucleotide sequence as it originates predominantly from metastatic breast cancer. So cadmium could be considered as a chemical carcinogen that may act either as initiator or promoter to mammary cells.

From the present data, there was no difference in the iron level as regards the tissue samples of the studied groups while there was a significant reduction of iron concentration in the urine samples of the cancerous group of patients, a finding that may be related to reduced total iron stores in female patients. This could be explained by the fact that pregnancy is known to gradually increase iron absorption during pregnancy that results in increased blood levels of iron [18].

In addition, increased cadmium concentration and decreased iron as women with low iron stores due to menstruation or vaginal bleeding disorders, suggesting a common mechanism of uptake for iron and cadmium through a duodenal metal transporter protein which is responsible for the uptake of iron into the mucosa cells and upregulated by iron deficiency and also for cadmium transport [18]. Thus, depleted iron stores and iron deficiency leads to increased cadmium uptake and increased cadmium accumulation.

Regarding copper, it was found to be increased in tissue samples and significantly increased in urine samples of cancerous patient. This finding was in accordance with previous studies which reported that copper has a close association with breast cancer [19-21]. We suggest

Group / Data	Non-cancerous group (n=25) N	Non-cancerous group (n=25) %	Cancerous group (n=75) N	Cancerous group (n=75) %	Odds ratios	95% confidence interval
Residence:					1.272	0.490 – 3.298
Rural	16	64	52	69.3		
Urban	9	16	23	30.7		
Smoking:					0.808	0.326 – 1.999
Smokers	0	0	0	0		
Passive smokers	13	52	35	46.74		
Non smokers	12	48	40	53.3		
Marital Status:					3.174	0.423 – 23.812
Married	23	92	73	97.3		
Single	2	8	2	2.7		
Oral contraception:					0.645	0.259 – 1.609
Used	13	52	47	62.7		
Not Used	12	48	28	37.3		
Parity:						
0-1	8	32	8	10.7	1	
2	6	24	15	20	2.5	0.53 – 12.3
3 or more	11	44	52	69.3	4.7	1.26 – 18.11
Menopausal status:					5.375	1.823 – 15.852
Pre-menopausal	20	80	32	42.7		
Post-menopausal	5	20	43	57.3		
Age of menopause (year):						
< 45	1	4	5	6.7	1	
45 – 50	4	16	29	38.7	1.45	0.72 – 1.54
50 – 54	0	0	9	12	1.2	0.84 – 1.72

Table 1: Demographic and reproductive data of patients in non-cancerous and cancerous groups.

Metals	Tissue samples		Urine samples	
	Non-cancerous group (mg/gm)	**Cancerous group** (mg/gm)	**Non-cancerous group** (mg/gm)	**Cancerous group** (mg/gm)
Cadmium				
Median	0.0665	0.1097↑*	0.0157	0.0790↑*
IQR	0.0099-0.1369	0.0085-1.573	0.000-0.2347	0.0077-2.0513
Iron				
Median	0.05895	0.06741	0.7462	0.01053*↓
IQR	0.2899-11.033	0.7080-21.461	0.0039-1.9883	0.3945-4.953
Copper				
Median	0.2380	0.5785	0.04013	0.1881↑*
IQR	0.0087-1.324	0.0462-7.258	0.0156-0.3506	0.0212-0.8967
Lead				
Median	0.0904	0.1204	0.0261	0.0296
IQR	0.0329-0.5270	0.0497-1.521	0.0181-0.0774	0.0173-0.1002
Zinc				
Median	0.01654	0.01671	0.4391	0.3081
IQR	0.1872-2.9178	0.5920-6.680	0.0252-1.0271	0.0877-1.572

*↑ significant increase ($p < 0.05$)
*↓ significant reduction ($p < 0.05$)
IQR: interquartile range

Table 2: Concentrations (mg/gm) of studied metals (Cd, Fe, Co, Pb, Zn) in tissue and urine samples of cancerous and non-cancerous groups (n=100).

the copper has a mechanism of action similar to cadmium in induction of breast cancer.

Furthermore, in the present work, lead had no significant difference between cancerous and non cancerous group but it was generally high in the tissue samples while zinc had no significant difference between studied groups. However, this finding differs from the finding of Ionescu [11] who demonstrated a significant increase in lead and zinc concentrations of patients with breast cancer. They accounted their effects to their ability to generate hydroxyl radicals leading to lipid peroxidation, DNA strand breaks and apoptosis.

As regards the socio-demographic data of the studied groups, highest incidence for developing breast cancer was detected in the Egyptian female patients who inhabiting rural areas, worked in farming which may indicate low socioeconomic status. These results differ from the American case control study that was done by Lannin [22] who stated that breast cancer was recognized as a disease that occurred more often among women of the upper social classes which may be related to increased incidence of non-married females and late age of first pregnancy.

Postmenopausal females were at higher risk to breast cancer especially those aged more than 45 years old. These findings supported the work of Antila [15] who reported that postmenopausal patients have increased risk of breast cancer as a result of reduction in progesterone levels and increasing cadmium concentrations by age. McElory [14] declared that postmenopausal females were at higher risk for breast cancer when associated with increased cadmium concentrations.

In non-occupationally exposed and non-smokers females, the most probable source for increasing cadmium was food intake as McElory [14].

The present findings agree with Järup and Åkesson [23] who stated that diet is the main source for environmental metal exposure and that metal contamination is present virtually in all foods. Abdel-Sabour [24] declared that Dakahlia governorate, Egypt showed high levels of cadmium; in the soil, water and subsequently fish and irrigated plants.

In an Egyptian study, Hassanien [6] had assessed human health risk estimates derived from potential metal inhalation of urban inhabitants by estimation of the distribution of toxic pollutants including primarily that of great risk for human health in atmospheric air samples collected from different regions in Cairo, Egypt. It was concluded that, the current levels of metals in air including cadmium were higher than those considered safe for the general population.

Kriegel [25] reported that River Nile and subsequently irrigated plants were seriously contaminated with heavy metals especially vegetables and fruits as cucumber and potato samples [5,26].

From the present result it could be concluded that the present study posits a causal association between cadmium and copper increase with reduction of iron and breast cancer.

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