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Appraisal of Trace Elements and Heavy Metals Levels in Breast Cancer Patients of Basrah Province

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Abstract

We know that metals are linked to a number of health problems such as constipation, abdominal pain, according to previous reports and lack of appetite, sickness, wakefulness, annoyance, irascibility, giddiness and encephalopathy. However, recent studies have found correlation between cancer and some toxic metals concentration in patients body. Most carcinogegenic metals are Cd, Pb and Hg. **Objective:** Current study was aimed to determine the concentrations of some metals(Cd, Pb, Hg, Cr, Cu and Zn) in whole blood, serum and hair of breast cancer patients in Basrah city, South of Iraq. **Methods:** Sample of whole blood, serum and hair were obtained from 60 breast cancer patients, the same samples were collected from 25 people without cancer as control group. Concentrations of heavy metals were carried out using ICP MS (an inductively coupled plasma atomic absorption spectrophotometer). **Results:** Concentrations of toxic metal such as Cd and Hg occurred at low level in three tissues while Zn occurred at higher concentrations. Pb concentration in the whole blood sample was 22.36 ug/l, Cr: 6.63, cu: 42.35.ug/g, serum of patients accumulating higher concentrations of Hg, Cr, Cu and Cd than in the whole blood sample. Even as Pb and Zn concentrations were high in whole blood. Conversely, hair sample of breast cancer patient accumulated significantly higher concentrations of Hg. Cr, Cu, Cd, Pb and Zn compared to other tissues. Positive correlations were recorded between Cd and Pb (r = 0.46), Zn with Cr, Cu and Hg (r = 0.78, 0.56, 0.88) respectively. **Conclusion:** High concentrations of Hg, Cr, Cu, Cd and Pb were detected in whole blood, serum and hair of breast cancer patients relative with other control group. Hair samples accumulated the high levels of Cd, Cu, Cr, Hg, Pb and Zn in comparison with whole blood and serum of breast cancer patients.

Keywords: Breast Cancer, Levels, Patient, Toxic Metals

1. Introduction

Speedy economic growth and industrialization were followed by an increase in chemical pollutants release into the environment, which resulted in contamination of the environment[1,2]. Heavy metals and trace elements can enter our bodies through respiration or food and water consumption. These elements can be excreted via hair, sweat, urine and feces or stored in organs such as the liver, kidneys and muscles[3,4].

Previous reports showed a close association between heavy metals and cancer[5] since these elements interrupt the body's pro-and antioxidant equilibrium. Therefore, biological monitoring by evaluating blood levels of certain heavy metals is being used to evaluate current intakes, absorption, transmission and elimination of certain metals[5]. Breast cancer is the second most popular type of cancer that results in women's death following lung cancer[6]. The incidence of breast cancer increases dramatically with aging and exists in postmenopausal women at much higher levels[6].

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The study of trace-heavy elements in human tissues has become of considerable interest in recent years due to their involvement in biochemical and physiological processes. Each of the critical and un-essential trace elements can be harmful if present in the cells, tissues or body fluids at high concentrations. Additionally, an excessive trace element presence might be involved in creating or progressing certain cancers[7,8]. Over the past 25 years, some heavy metals such as cadmium, nickel, arsenic, beryllium and chromium were marked as human or animal carcinogens as reported by the International Cancer Research Agency (ICRA) and the National Toxicology Program (NTP)[9]. High contamination rates have been observed in southern Iraq after the 1991 invasion and the latter in 2003. Cancers and idiopathic congenital abnormalities were among diseases whose hazard increased as a result of this contamination[10].

The aim of this study was to determine the concentration of heavy metals Cd, Pb, Hg, Cr, Cu, and Zn in three biological samples types, including whole blood, serum and hair of women with breast cancer and to determine the relationship between metal levels and cancer improvement.

2. Material and Methods

2.1 Study Groups

Samples were collected from confirmed breast cancer cases at the oncology center of Al-Sadr Teaching Hospital in Basrah City. This center is the only one in Basrah to deal with adult cancer patients. The patient group consisted of 60 females. The patients' ages ranged from 30 to 70 years, average of patients old (49.68 ± 12.03). The comparison group consisted of 25 healthy individuals with no chronic disease ranging between 20 and 60 (42.81 ± 15.78).

Blood serum and hair samples were collected from each individual of both groups between October 2019 and March 2020 (ethical approval from the director of the Human Development Center at the Basra Health Department Issue 490, 3 Sep.2019). Additionally, personal information was collected from each case of each group. The collected information concentrated on residency placement within the studied area (Basrah city), employment background and social status. Patients with a positive family history of breast cancer were governed out of the study.

2.2 Laboratory Experiments

Blood samples (5 ml) were collected from subjects with a sterile disposal syringe. From each collected sample, 2 ml whole blood sample was transferred to a tube containing anticoagulant and the remaining was kept in a tube without anticoagulant in order to obtain serum after centrifugation at 3000 rpm for 15 minutes.

In a flask, 4 ml of nitric acid (70%) and hydrogen peroxide were added to the whole blood sample and digested on a hot plate at 150^{0}C under a fume hood gently below the melting point for 4 hours. Once the volumes were decreased by about one third and the solution was transparent, deionized water was applied to complete the volume to 25 ml. Afterwards, the solution was filtered using filter paper no. 1. Samples were transferred to 50 ml plastic container tubes for analysis[6].

Hair samples were collected from the back of the head as close as possible to the scalp by stainless steel scissors on the nape of the neck (2-3 cm from the skin), taking into account the average hair growth rate between 0.6 and 3.6 cm per month[11]. The samples were transferred immediately to sealed plastic bags and marked with the donor information. For rapid digestion, the hair samples were cut into small pieces of about 1 cm or less and soaked for approximately 10 minutes in deionized water. The samples were washed with acetone and dried in an oven at 110^{0}C for 1 h[12]. The steps for digesting the blood samples were applied and the digested samples were stored at a temperature of 20^{0}C until analysis.

Inductively coupled plasma mass spectrometry (ICP-MS) NexION 300D was calibrated and each hair, blood or plasma sample was analyzed twice (duplicates). Standards and blank samples were analyzed with test samples.

2.3 Statistic Analysis

All computations were carried out using SPSS (V19.0, SPSS Ltd., Woking, Surrey, UK). The inferential statistics (mean values, standard deviation) for metal concentration principles were evaluated through one-way variance analysis preceded by Tukey's honestly significant difference LSD. Variations at the $p<0.05$ level were deemed significant. t-test was used to compare between patient group and control group with 95% Confidence Interval (CI) of the difference. 2-tailed Pearson's correlation coefficient was also calculated at $p<0.05$ and $p<0.05$ to detect possible correlation among metals concentrations in the tissues.

3. Results

3.1 Phytochemical Screening Test

The demographics distribution of patients indicated that the center of urban residents and married women were at higher risk of developing breast cancer, while it was noticed

that the lowest cancer patient percentage was of those living in the outskirts of the city and unmarried (Table 1). 46% of breast cancer patients lived in the center of Basrah, while 30% and 31% were located in the north and south of the city. The majority of breast cancer patients were married (86.6%). The age group with the highest proportion of breast cancer patients was 40-50 with 31.8%, while the lowest percentage was observed among those between 20 and 30 years with 6.6% (Table 1).

Table 1. Data of patients with breast cancer and non- cancerous person

Patients without cancer 25	Patients with cancer 60		Patients without cancer 25	
	No.	%	No.	%
Resident			3	12%
North Basrah	18	30%	5	20%
South Basrah	19	31.6%	16	64%
Center of Basrah	28	46.6%		
Social status				
married	52	86.6%	14	56%
unmarried	8	13.3%	11	44%
used for deodorants	22	36.6%	15	60%
not used for deodorants	38	63.3%	10	40%
Age groups				
20-30	4	6.6%	6	24%
30-40	9	15%	9	36%
40-50	19	31.8%	5	20%
50-60	17	28.3%	3	12%
60-70	11	18.3%	2	8%

3.2 Concentration of Heavy Metals in Biological Tissues

The concentration of six heavy metals (Cd, Hg, Pb, Cr, Cu and Zn) was measured in the total blood, serum and hair samples of cancer patients and normal group members. In general, the toxic metals Hg and Cd presented in fewer concentrations in three tissues when compared to Pb, Cr, Cu and Zn. On the other hand, zinc concentration was the highest in all sample types (Table 2).

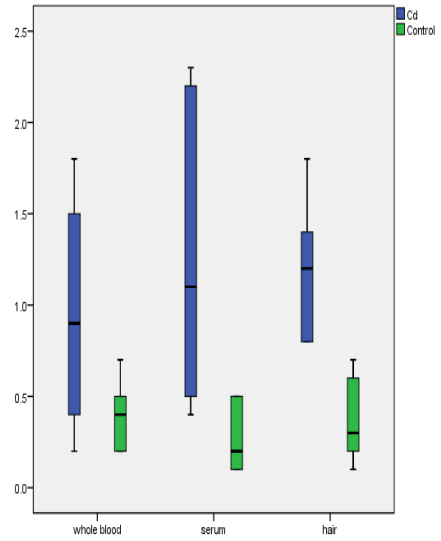
The concentrations of Cd, Hg and Cr in serum samples of cancer patients were 1.26, 1.36 and 12.2 ug/l, respectively. These concentrations were higher than those in whole blood, while concentrations of Pb, Cu and Zn decreased in the serum compared to whole blood. The concentration of all metals except Cd and Pb in the hair samples of breast cancer patients was significantly higher than those presented in the whole blood and serum samples. When comparing the concentration of heavy metals between breast cancer patients and control group, it was noticed that Cd concentration was substantially higher in the former group compared to the latter for all sample types (Figure 1 A). Furthermore, the concentrations of Cr, Cu, Hg and Pb in breast cancer patients have significantly increased in whole blood, serum and hair of cancer patients (Figures 1 B, C, D and E). On the other hand, there were no significant differences in Zn concentration between the control and breast cancer patients (Figure 1 F).

A positive correlation was observed between Cd and Pb concentrations ($r = 0.468$). Cr concentration significantly correlated with each of Cu, Hg and Zn with correlation coefficients of 0.48, 0.79, and 0.78, respectively. Furthermore, the concentration of Zn significantly correlated with Cu levels ($r = 0.56$) and Hg ($r = 0.88$).

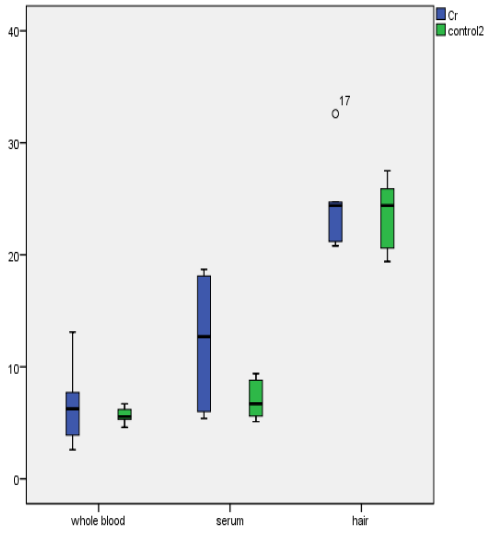
Table 2. Concentrations of heavy metals (mean ± SD) ug/L in whole blood, serum, hair of breast cancer patients

Heavy metals		Cd	Cr	Cu	Hg	Pb	Zn
whole blood	Mean	.9500	6.6333	42.3500	.4667	22.3667	426.0833
	Std. Deviation	.69210	3.75855	18.01796	.29439	11.46955	76.39590
serum	Mean	1.2667	12.2667	23.7833	1.3667	16.3333	279.3000
	Std. Deviation	.82624	5.69620	6.01379	.87560	10.91397	125.83030
hair	Mean	1.2000	24.6833*	53.6333*	4.9667*	21.8167	1880.650*
	Std. Deviation	.40000	4.24566	15.69238	1.78064	12.78193	461.18209

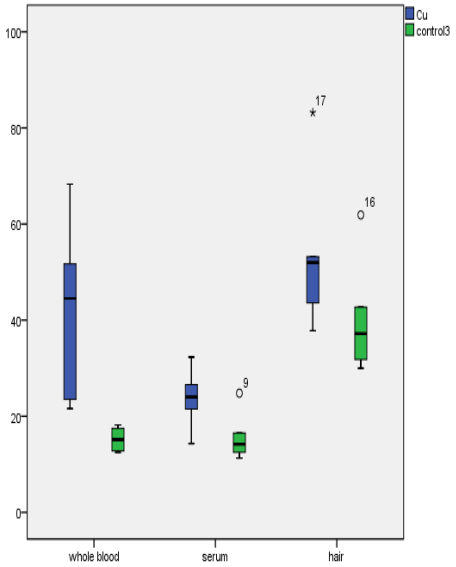
*the mean difference is significant at the 0.05 level between tissues



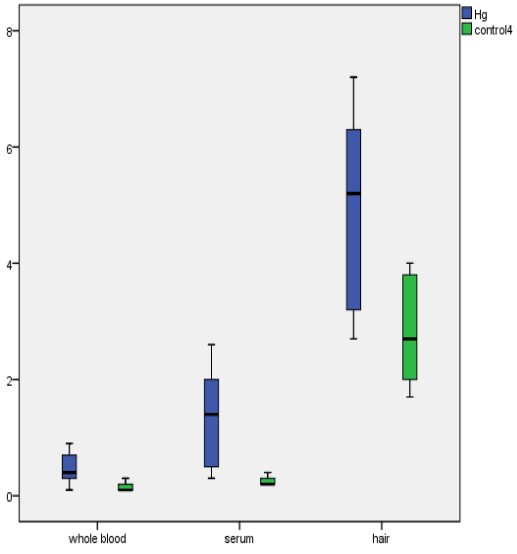
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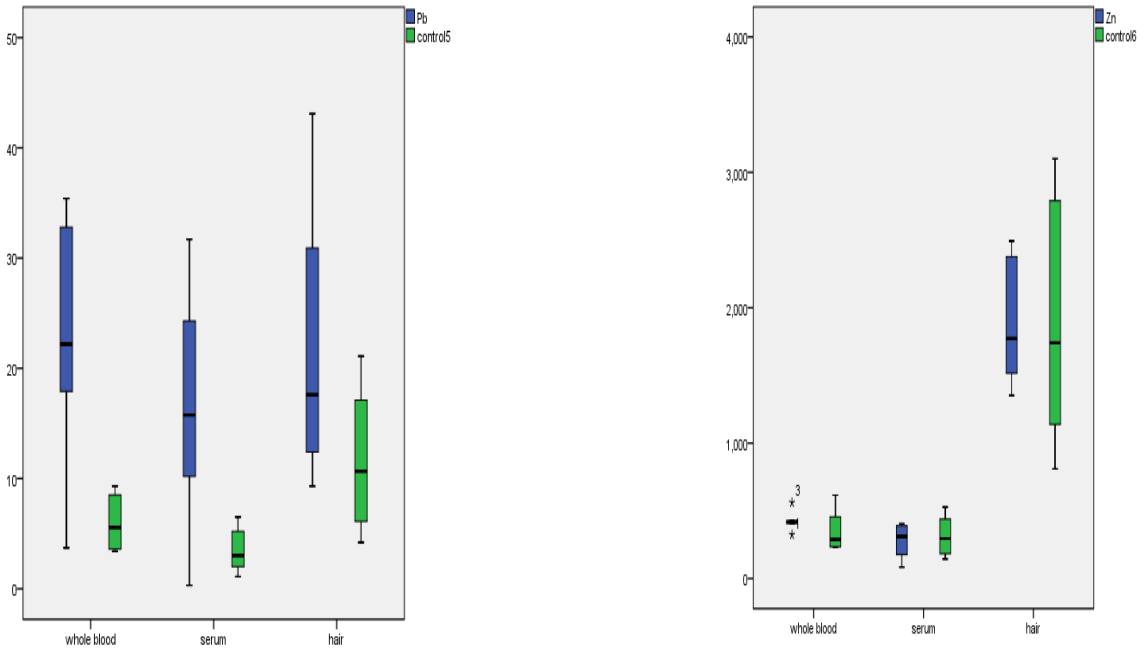
B



C



D



E F

*The mean difference is significant at the 0.05 level (t-test was used to compare between patient group and control group with 95% Confidence Interval (CI) of the difference.

Figure 1. Concentrations of six metals (ug/l) in whole blood, serum and hair of patients with breast cancer compare with control groups (non-cancerous group) A: Cd* ,B: Cr ,C: Cu *, D: Hg*, E: Pb* and F: Zn.

4. Discussions

Humans usually need trace amounts of heavy metals such as cobalt, copper, iron, zinc and vanadium in their diet[13]. The evaluation of heavy metals and trace elements in human tissues is an essential indicator of human health status or disease. There is no awareness of valuable or adverse connections between serum or blood trace elements levels and breast cancer. Some ecological and nutrient conditions may produce estrogenic or carcinogenic effects that influence breast cancer[14]. In this study, the levels of six trace elements in blood, serum and hair samples from Basrah women with breast cancer and women with no breast cancer were evaluated. Data from breast cancer patients showed that cancer cases were more concentrated in Basrah city center, with 46.6% of total cases. On the other hand, the rest of the cases were almost equally distributed between the southern and northern parts of the city. A higher proportion of married women with breast cancer than single women were also noticed. Some reports contend that marital status does not affect this malignant disease[15], while other epidemiological studies have found higher breast cancer rates in unmarried women than in married women[16,17]. Marital status can interact with the risk of developing breast cancer amongst women. However, inadequate control collection, inadequate investigation of conflicting results, insufficient marital status evaluation and potential publication bias may have restricted the credibility of the collected data. Therefore, findings could not be drawn that marital status is an autonomous risk factor for breast cancer. Thus, the requirement of rigorous cohort studies is justified.

The age group of 40-50 years of age had the highest breast cancer rate (31.8%), followed by 50-60 years, while the age group with the smallest number of cancer cases was 30-40 years, with only 4.5% of total cases. Postmenopausal women, in particular those over 45 years of age, were at higher risk for breast cancer. These results confirmed the research of[18,19] who reported that postmenopausal women had an increased breast cancer risk due to decreased progesterone rates and increased age-specific cadmium concentrations.

Disparities in the concentration of trace minerals between various populations may be affected by geographic location, cultural traditions, contamination and genetics of the body[20]. As in (Table 3) the results showed that the concentration of Zn was significantly higher than the other six metals, while Hg was found at low concentrations. Comparing different tissues, hair of patients accumulated higher Cr, Cu, Hg and Zn concentrations compared to blood and serum. Serum of cancer patients had significantly higher concentrations of zinc, lead and cooper than non-cancer individuals and fewer cadmium concentrations. Another study by[21] found high Serum manganese and molybdenum in breast cancer patients than control.

Table 3. Person correlation between heavy metals concentrations in whole blood, serum and hair of breast cancer patients

	Cd	Cr	Cu	Hg	Pb	Zn
Cd	1	-.038-	-.069-	.083	.486*	.028
Cr	-.038-	1	.487*	.798**	-.110-	.780**
Cu	-.069-	.487*	1	.382	.109	.569*
Hg	.083	.798**	.382	1	.077	.883**
Pb	.486*	-.110-	.109	.077	1	.129
Zn	.028	.780**	.569*	.883**	.129	1

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

The interaction between trace minerals and the etiology and development of cancer has also been widely studied, with conflicting findings[22]. Cr concentration in the current study was 12.2 ug/g in the serum of breast cancer patients. This result was higher than previous studies like[21] and[22] but less compared with[23]. Cu concentration was 23.7 ug/l in the serum of breast cancer patients, which was less than its levels in the blood and hair of patients. Cu concentration was higher than the levels previously reported in similar studies of breast cancer in Korea, Nigeria, Taiwan, Canada, India, China and Kuwait[21,23-30]. However, no major variations in Zn levels were reported between the cancer patient and control, similar to the findings of a study conducted in Korea[21] and another performed in Canada[26]. Although there were generally no significant differences in lead concentration between the two groups for all the studied tissues, lead level was substantially higher in cancer patients samples compared to non-cancer population. This result differs from[31], who showed no significant increase in lead and zinc concentrations in breast cancer patients.

The average concentrations of cadmium in breast cancer patients ranged between 0.9 and 1.2 ug/g varied considerably from that of control. This result is contrary to[18], who found no substantial variations between Cd concentration in breast cancer patients and control. That might indicate that cadmium binding proteins are present in human breast tissue. Previous researchers reported that Ni and Cd might mimic the estrogens' actions and disturb the body's endocrine function resulting in the production of metalloestrogens[32]. An analysis study found that divalent cations and metal/metalloid anions are contained in metal estrogens such as Cd and Ni, thus, exposure to certain metals might increase the risk of breast cancer[32].

5. Conclusion

Various tissues had different amounts of heavy metals. Comparing blood, serum and hair showed that hair could accumulate high levels of all heavy metals (Cd, Cu, Cr, Hg, Pb and Zn). Additionally, higher levels of the aforementioned heavy metals were observed in cancer patients' tissues than control. Among the studied heavy metals in patients' tissues, Zn existed in the highest concentrations, while the lowest levels were of Cd. Patient demographics distribution indicated that the center of urban residents and married women were at higher risk of developing breast cancer, whereas the percentages of cancer patients living in the city's outskirts and of unmarried women were the lowest. The current research shed light on the possible functions and implications of trace element by analyzing the interactions between trace elements and breast cancer occurrence. The previous research and the current analysis of the relationship between trace elements and cancer pathophysiology had offered conflicting findings. Therefore, further studies are required to assess the interactions between heavy metal levels in serum and other tissues, treatment of nutrients, and care results for further understanding

6. Acknowledgement

We thank the Director of the Cancer Center at Basra Teaching Hospital and the staff at the central laboratory in the hospital for their cooperation in collecting samples.

7. Declaration on Conflict of Interest

No conflict of interest

8. Ethical Approval and Consent to Participate

We have ethical approval from the director of the Human Development Center at the Basra Health Department Issue 490, 3 Sep 2019.

9. Consent for Publication

All authors consented for publication.

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