

Role of Some Trace Elements in Breast Cancer Receiving Chemotherapy

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Abstract : This study aim to examine changes in serum concentration of trace elements; cobalt (Co), germanium (Ge), molybdenum (Mo), nickel (Ni), vanadium (V), and magnesium (Mg) in breast cancer patients and control group, in addition to establish of databases in the Iraqi population. The study was included 40 patients with breast cancer and 50 healthy subjects. Serum concentrations of trace elements were measured by flame atomic absorption spectrophotometer. Statistical analysis of data demonstrated significant decrease ($p < 0.001$) in Co, Ge and Mg concentrations in patients with breast cancer when compared with healthy. The study showed a significant increase ($p < 0.001$) in Ni and V concentration in patients with breast cancer when compared with healthy. The results showed no change in concentration of Mo in breast cancer patients as compared to healthy. In conclusion, essential elements Mg and trace elements Co, Ge, Ni and V may play a central role in the pathogenesis of breast cancer.

Key words: Trace elements, Mg, Co, Ge, Ni, V breast cancer, , atomic absorption spectrophotometer.

Introduction

The specialized cancer agency of the World Health Organization; the International Agency for Research on Cancer (IARC) released on 12 December 2013 the latest data on cancer statistics worldwide. The IARC's database, take about 14.1 million new cancer cases and 8.2 million cancer deaths in 2012¹.

Cancer is a significant and a major health problem all over the world. Iraqi reports found that at least 350 people in Babylon province/Iraq alone were affected by cancer every year². Cancer is a cellular disease caused by mutation or abnormal activation of cellular genes responsible in control cell growth and mitosis³, with different types that vary from one another⁴.

Breast cancer is the most common cancer detected in women throughout the world²; and a second most common cancer in the world-wide with 1.7 million new cases per year which represent 11.9% of cancer cases¹.

Breast cancer is caused by genetic factors (about 5-10% of breast cancer are hereditary) or hormonal factors (prolonged estrogen exposure) and many other risk factors such as late first pregnancy, obesity in postmenopausal women (about 50%) and alcohol intake⁵. Other environmental carcinogens included radiation, organic chemical (tobacco smoke) pollutants like exposure to metals, dust, nickel, uranium and others^{3,4}.

The immunity of the human body is the natural mechanism that protects against cancer. Trace elements represent vital processes in human health and disease in contributing in cellular and subcellular function, including immunoregulation by both humoral and cellular immunity⁶. In addition, trace elements considered

anticarcinogenic agents by its antioxidant potential dependent enzyme, induction metallothionein, DNA repair and alteration of carcinogen metabolism⁷.

Cobalt (Co) is nutritionally essential metal as a part of vitamin B₁₂ or cobalamin⁸. It is found in very low levels (less than 0.1mg/kg) in food, the highest in nuts and yeast extract. Since it is a fundamental part of cobalamin, a deficiency of these rare elements (0.001% of the lithosphere) probably causes pernicious anemia⁹. Co is necessary for the synthesis of thyroid hormone and beside iodine and other chemical elements found to influence thyroid goiters and then cancer¹⁰. Physiological concentration of Co acts as cardioprotective while high dosage of Co may cause cardiac failure¹¹. Co could be carcinogen; the mechanism of gene mutation by Co is DNA breaks and inhibition of DNA repair¹².

Germanium (Ge) is ultra trace element found naturally in very low concentration in food, especially meats and described as an antioxidant and anticancer agent¹³. Its rich sources are wheat bran, vegetables and leguminous seeds. Ge occurs mainly in the human body in the bone (9μg/g), liver (0.3μg/g) and pancreas (0.2μg/g) and it has been considered non-essential trace element as its molecules of biological importance is none identified¹⁴. Ge has believed to drop blood pressure and excite immunity to inhibit rheumatoid arthritis¹⁵. Lück *et al.*¹³ mentioned that intake of Ge compounds causes renal failure, liver dysfunction and anemia.

Molybdenum (Mo) is nutritionally essential metal accumulated in the human body in liver, kidney, bones and skin¹⁴. Several enzymes contain Mo including xanthine oxidase and xanthine dehydrogenase; necessary for the uric acid formation, and involved in purine degradation⁹. All foods and beverages (even water) contain Mo^{9,14}. Mo deficiency could be a reason for forming esophageal cancer^{6,16}, development of thyroid goiters and cancer and associated with sexual impotency and tooth decay¹⁰. Mo is considered as anti-cancer¹⁶.

Nickel (Ni) is a trace metal with potential advantage effects⁸ which has the ability to bind to many organic compounds of biological concern, including amino acids; especially histidine and cysteine, and protein mainly albumin^{9,14}. Ni levels in food are low and can be seen in dried tea leaves, cacao beans and nuts⁹. Ni mainly found in the adrenal glands, bones, kidney and thyroid. It has a role as a cofactor in the metabolic pathway of vitamin B₁₂ and folic acid¹⁴, and involved in the regulation of methionine-folate cycle¹⁷. Ni has been considered as important carcinogen¹⁸. Nickel deficiency status includes a change in skin color, hormone imbalance and abnormal bone growth [15], and low growth and reproductive action¹⁹.

Vanadium (V) is a micronutrient element that has an important and distinctive role in human metabolism, found in cereals, meat, fish, vegetables and milk with daily intake about 10 μg-2mg⁹. High content of V in the body exists in bone, kidney, liver, spleen and testis, V have been believed to use iron transport system and bone is a storage part for excess vanadium¹⁴. It's important for bone, glucose and cholesterol metabolism and affect thyroid and the dentin of tooth, high dose intake of V could cause vitamin C diminution¹⁵. It has been mentioned that V can alter the activity of Na/K-ATPases involved in muscle contraction. Deficiency of V has been related to impaired reproduction and altered genesis of red blood cells and iron metabolism⁹. Also, Cesar⁸ and Jaryum *et al.*¹⁹ mentioned that V deficiency can cause skeletal deformities and increasing of thyroid weight.

Magnesium (Mg) is an essential major mineral found in the human body as a part of several enzymatic processes in intra- and extra- cellular components²⁰, about 300 enzymatic reactions involve Mg: it plays an important role in the stabilization of ATP and other molecules, glycolytic cycle, oxidation of fatty acids, protein synthesis^{15,21,22} and also plays an important role in carbohydrate metabolism²³. Mg is important in bone development and maintenance of bone, about 60% of Mg exists in bone^{14,21}, 38% in the skeletal muscle and liver, and less than 2% is in the extracellular fluid²⁴. Mg provides elasticity to prevent injury and act with calcium to assist in muscle contraction, blood clotting and thought to regulate blood pressure²². Deficiency of Mg mentioned to be a contributor of tetany, calcium deficiency, and development of cardiovascular disease, diabetes mellitus and hypertension^{14,15}. Mg deficiency is more widespread in cancer patients than others²⁴.

Current study aim to examine changes in serum concentration of trace elements in patients with breast cancer and control group, in addition to establish of data bases in the Iraqi population.

Materials and Methods

Materials

This study was approved by the Local Ethical Committee. All persons participated in the present study were agreed to participate and signed an informed consent.

The diagnosis of patients was done according to clinical identification of physician in an Oncology Unit at Merjan Teaching Hospital in Hilla city and clinical analysis.

A random blood samples of 40 patients with breast cancer admitted to the Oncology Unit at Merjan Teaching Hospital in Hilla city in Iraq were collected as well as 50 healthy subjects according to standard procedure and the sera obtained were stored at -20°C until the day of analysis. Table 1 illustrates the participants number and their mean age.

Table 1: Number and age of patients and healthy subjects.

Mean age (year)	No.	Subjects
31.14 ± 9.4	50	Healthy
46.1 ± 5.6	40	Breast cancer

Treatment Regime

Breast cancer patients treated according to Herdrich and Weinberger²⁵. Patients with breast cancer were receiving chemotherapy regimen: doxorubicin 60 mg/m^2 or cyclophosphamide.

Trace element analysis

Serum concentration of Mg, Co, Ge, Mo, Ni and V were measured by using Shimadzu AA-700 atomic absorption spectrophotometer after digestion the sera with concentrated nitric acid and concentrated perchloric acid, then analyzed by instrument according to the procedure described previously^{8,26}.

Statistical analysis:

All data were subjected to t-test: two sample assuming unequal variance to determine the level of significance between healthy and patients with breast cancer, and the value of $p \geq 0.05$ was considered statistically significant. Data are expressed as mean \pm standard deviation (\pm SD).

Results

Concentration of trace elements

The results of concentration of trace elements (Co, Ge, Mo, Ni and V) in serum of patients with breast cancers as compared with healthy subjects are presented in Table 2.

Table 2: Concentration of trace elements in sera of patients with breast cancer and healthy subjects.

V ($\mu\text{mol/L}$) \pm SD	Ni ($\mu\text{mol/L}$) \pm SD	Mo ($\mu\text{mol/L}$) \pm SD	Ge ($\mu\text{mol/L}$) \pm SD	Co ($\mu\text{mol/L}$) \pm SD	Subjects
0.0090 \pm 0.0010	0.0106 \pm 0.0014	0.0104 \pm 0.0029	0.0512 \pm 0.0198	0.03955 \pm 0.0055	Healthy
0.0107 \pm 0.0021	0.0125 \pm 0.0022	0.0100 \pm 0.0027	0.036 \pm 0.0080	0.0115 \pm 0.0014	Breast Cancer
0.0011	0.0009	0.061	0.0007	0.0001	p-value

Concentration of Mg

Table 3 revealed significant increase ($p < 0.001$) in a concentration of Mg 12.69 ± 0.01 in patients with breast cancer and as compared with healthy subjects ($18.77 \pm 2.10 \mu\text{mol/L}$).

Table 3: Concentration of Mg in sera of patients with breast cancers as compared with healthy subjects and.

Mg ($\mu\text{mol/L}$) \pm SD	Subjects
18.03 ± 1.42	Healthy
12.69 ± 0.01	Breast Cancer
0.00084	p-value

Discussion

The results of this study signify that serum Co concentration were decreased in patients with breast cancer whose receiving chemotherapy which agree with other research by Arooj *et al.*²⁷. Deficiency of essential elements Co may cause vitamin B₁₂ deficiency since it is part of vitamin B₁₂⁹.

The data informed significant decrease in serum concentration of Ge in patients with the breast cancer whose receiving chemotherapy. Ge deficiency could be a risk factor of cancer since Ge represents a powerful antioxidant against cancer by means of its activity to slow down the multiplication process of cancer, hence inhibit tumor growth and enhance natural killer cells to act on²⁸.

Braverman and Pfeiffer⁶ mentioned that deficiency of Mo in the human body could be a proper cause of another type of cancer like esophageal cancer. Mo deficiency seemed to be one of the risks and causative factor of gastric cancer²⁹. Mo is thought to prevent body against cancer through augmentation the mechanisms of natural immunological diminution of cancer⁶. Molybdophosphate could be used as anticancer therapy¹⁶.

According to the results of this study, serum concentration of Ni were significantly increased in breast cancer patients receiving chemotherapy. This is supported by previous studies³⁰ which were found increased serum Ni concentration in patients with bladder cancer. Ni level in saliva of oral cancer patients was high as a contrast with healthy people⁷. Ahmed *et al.*¹⁸ mentioned increased Ni concentration in esophageal cancer patients may play some role in carcinogenesis in preventing the intracellular communication and induces DNA deletion. In addition to Ni, V was significantly increased in breast cancer patients receiving chemotherapy. V possibly exert an effect on oncogenesis since it is also interfering with proper chromosome arrangement during cell division¹².

Mg is essential major mineral in the human body as a part of 300 enzymatic processes^{15,21,22}. The data of this study showed significant decrease in serum concentration of Mg in patients with breast cancer who's receiving chemotherapy which agree with another previous research in thyroid cancer patients³¹. Koyama⁷ found significant reduction in the Mg level in saliva of oral cancer patients. In addition to cancer effect on Mg, anticancer drugs, especially cause hypomagnesemia in cancer patients²⁴. Therapy with cytotoxic drugs may have impaired renal tubular reabsorption of Mg causing its loss in urine³². Mg deficiency may trigger carcinogenesis by increasing membrane permeability of cancer cells, high level supplemented Mg inhibits carcinogenesis²⁸.

Conclusions

Trace elements are essential in the human body and play important roles in many enzymatic metabolism. In conclusion, the decrease in Ge levels which act as antioxidant, increases oxidative stress that in turn may lead to cancer. The decrease in the Mg level leads to increase membrane permeability of cancer cells that may trigger carcinogenesis. The decrease in Mo leads to decrease in immunity of the body which may lead to cancer, as well as compound of Mo act as anticancer. The decrease in Co levels leads to B₁₂ deficiency anemia that associate with cancer and one of cancer consequence. Whereas, the increase in Ni levels induces

DNA deletion which leads to cancer. Also, the increase in V levels increases oncogenesis due to interferes with proper chromosome arrangement during cell division that may lead to cancer. Figure 1 summarizes conclusions of the present study.

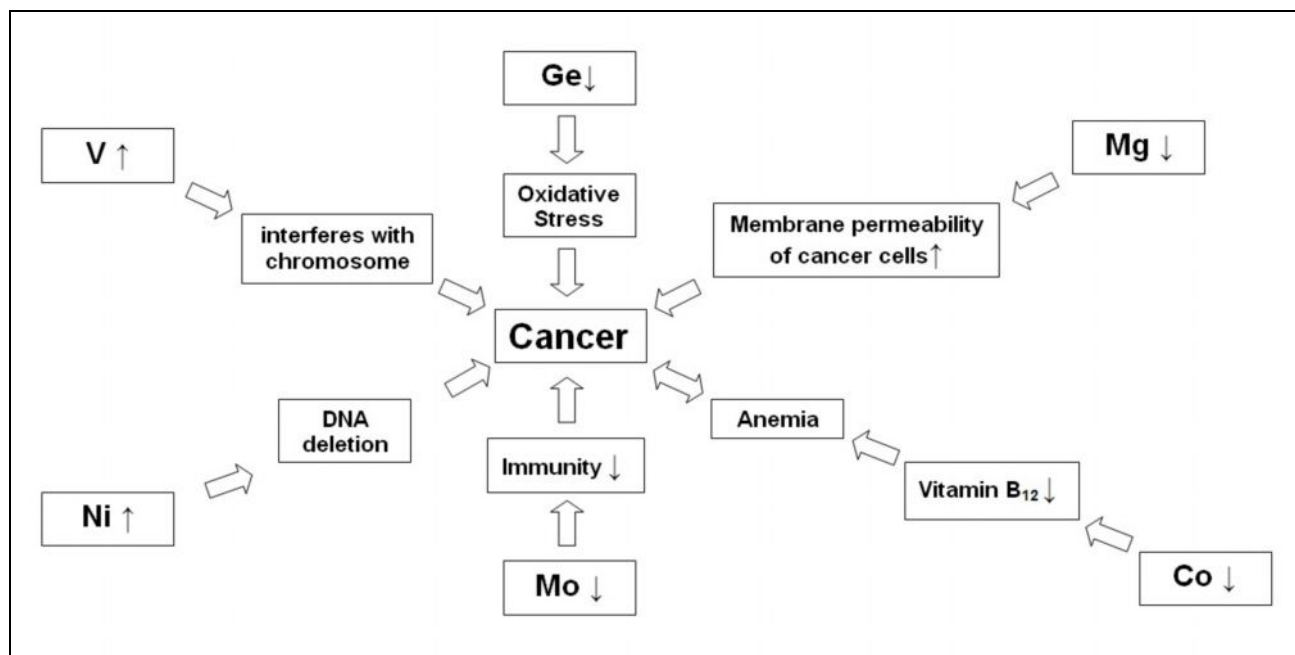


Figure 1 summary of the role of some trace elements in the pathogenesis of cancer.

↑ mean increase, ↓ mean decrease.

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Conflict of Interest

No conflict of interest exists in this study.

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