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ELEMENTAL STATUS OF WOMEN SUFFERED FROM BREAST CANCER

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ABSTRACT: Multielement hair analysis of 52 postmenopausal women was carried out. Possible significance of Zn, Cu, Se in women with progression of cancerous process (T2N0M0, T3N1M0, T4N1M1) was observed. The minimal hair Se was typical for patients after mastectomy while the maximal hair Se and lowest Cu level was found in firstly evaluated patients (T1N0M0) (Zn, Cu, Se deficiencies were suggested to be a risk factor for the development of breast cancer). Suboptimal provision of postmenopausal women can decrease the anti-tumour defense mechanisms. This is why the adequate Zn, Cu and Se consumption in menopausal and postmenopausal women is very important.

Introduction

Breast cancer comprises 23% cases of human tumors. It is characterized by the highest rate of mortality and disablement among oncological diseases. According to world statistical data, abundance of newly detected cases of breast cancer amounts 75.5 per 100000 women (Spyron, 1983). Breast cancer is a multifactor disease. Age, geographical and ethnic peculiarities, social status, nutrition, family status, number of children in the family, hormonal activity, exposition to radiation, heredity, presence of benign tumors in mammary glands are the factors most often mentioned as the risk factors of breast cancer (Cramer et al., 1986).

Role of major and trace elements in carcinogenesis is an interesting aspect of the problem. Thus, some investigations concerned participation of copper in development of neoplastic process and immune reactions as a whole (Chandra, 1985; Pocino et al., 1991). High level of Cu is observed in tumor tissue, being accompanied by increase of the element's concentration in blood serum (Aspin, Sass-Kortsak, 1983; Margalioth et al., 1983). On the contrary, tumor growth progression leads to decrease of Cu level in tumor tissue (Mikhaleva et al., 2002). Selenium is an important factor of breast cancer development due to its activating influence on glutathione peroxidase, a key enzyme of antioxidant defence in the organism. Epidemiological studies showed that lack of selenium in diet coincides with high frequency of breast cancer, skin cancer and cancer of ovaries (McConell et al., 1980). However in postmenopausal women, suffering from breast cancer, high level of Se in nails is described (Mannisto et al., 2000). Role of iron in carcinogenesis is intricate. According to some literary data, intensity of ferritin synthesis determines proliferative activity of tumor cells while the inability to ferritin synthesis leads to apoptosis of tumor cells (Poljak-Blaži, 2002). Excess of free iron enforces lipid peroxidation, and tumor cells survive worse under conditions of oxidative stress (Bergeson et al., 1985). Influence of zinc on immune reactions, especially on T-cell immunity, phagocytic activity of leucocytes, their maturation and differentiation in thymus, is well-known (Prasad, 1995). Low level of Zn is detected in nuclear fraction of tumor cells (Feustel, Wennrick, 1984). Simultaneous decrease of Mg, Ca and Zn concentrations is found in hair of women after mastectomy (Wojciak et al., 2002).

Participation of toxic elements in development of the neoplastic process is most often considered under conditions of its increased intake into the organism. Determination of toxic elements content directly in tumor tissue of mammary gland showed accumulation of Al, Rb as compared with intact tissues, while analogous analysis of the affected tissues of ovaries showed accumulation of Al, Ni and decrease of Pb concentration (Spyron, 1983; Mikhaleva et al., 2002).

Materials and Methods

Investigation of major and trace element concentrations in hair of postmenopausal women was carried out. The women were divided into four groups. The group I consisted of 13 persons, aged of 50 to 80 years, with newly detected breast cancer T1N0M0 according to international classification. The diagnosis was verified on the basis of mammography data and histological investigation after surgical treatment. The group II contained 11 women of 49–75 years old with progression of tumor process (T2N0M0, T3N1M0, T4N1M1). The group III

consisted of women of 50–76 years old, went through mastectomy for breast cancer 2–7 years ago (n=38). The group IV was the control group (n=25).

Hair samples were collected and treated in accordance with IAEA and Russian Ministry of Public Health recommendations (Methodical recommendations, established by Federal Center of Sanitary-Epidemiological Service of Ministry of Public Health of Russian Federation 29/01/2003).

Hair samples were taken from 3–5 places of scalp occipital zone. Proximal parts of hair strands 3–4 cm long were used for analysis. Hair (0.2–0.5 g) thus cut was immediately placed in special bags, which were then accurately sealed and labeled with a group number, the subject name, and the date.

All specimens were stored in dry, cool and ventilated environment until delivery to the laboratory and then kept in desiccators until analysis.

Hair samples were cut in pieces no longer than 1 cm, processed by acetone (ex.p.) in 10–15 minutes, and then washed thrice by double distilled water. After that they were dried at 60°C till air-dry condition. Then 0.1 g of the dried hair was used for analysis. Hair digestion has been carried out in plastic test-tubes by wet ashing with nitric acid on a balneum within 1 hour.

Analytical determination has been carried out by atomic emission spectrometry with inductively coupled argon plasma (ICP-AES) method using Optima 2000 DV (Perkin Elmer, USA) spectrometer.

Table 1. Average concentrations (mg/kg, M±m) and proportions of some chemical elements in women's hair.

Element	Group 1 (n = 13)	Group 2 (n = 11)	Group 3 (n = 38)	Control group (n = 25)
Al	25.77±4.73	20.16±3.97	19.72±3.19	19.89±1.9
As	0.15±0.07	0.13±0.1	0.2±0.1	0.38±0.05
Be	0±0	0.02±0.02	0±0	0±0
Ca	1010.4±263.45	925.23±244.24	1094.37±215.89	1332±172.33
Cd	0.06±0.02	0.08±0.02	0.21±0.11	0.13±0.02
Co	0.22±0.04	0.19±0.06	0.11±0.06	0.14±0.02
Cr	0.58±0.07	0.62±0.15	0.65±0.24	0.75±0.08
Cu	9.82±1.13	10.3±1.69	11.11±0.91	13.72±1.79
Fe	16.25±2.58	19.65±3.64	30.01±7.79	23.52±3.01
K	508.36±197.15	987.65±806.35	1500.82±975.13	231.85±54.84
Li	0.04±0.01	0.06±0.02	0.03±0.01	0.04±0.01
Mg	75.8±19.24	102.3±37.24	113.3±24.61	98.28±11.91
Mn	0.91±0.2	1.11±0.38	1.09±0.25	0.97±0.16
Na	580.21±223.3	474.59±87.62	719.45±321.08	606.34±176.83
Ni	0.27±0.08	0.49±0.24	0.63±0.14	0.55±0.1
P	154.88±8.33	166.84±15.5	154.05±13.47	198.24±21.02
Pb	0.43±0.12	0.57±0.22	0.79±0.25	0.95±0.21
Se	3.36±1.65	1.84±0.36	0.61±0.2	1.35±0.16
Si	23.19±11.87	15.52±3.16	30.41±13.82	31.29±4.98
Sn	1.09±0.38	1.37±0.36	0.37±0.13	2.06±0.73
Ti	0.51±0.14	0.89±0.33	0.82±0.12	0.38±0.06
V	0.09±0.03	0.08±0.02	0.04±0.01	0.16±0.02
Zn	162.11±14.68	158.05±13.08	164.46±12	189.95±7.44
As/Se	0.04	0.07	0.33	0.28
Cu/Fe	0.60	0.52	0.37	0.58
K/Na	0.88	2.08	2.09	0.38
Cd/Se	0.02	0.04	0.34	0.10
Cd/Zn	0.00	0.00	0.00	0.00
Mg/Pb	176.28	179.47	143.42	103.45
Ca/Pb	2349.77	1623.21	1385.28	1402.11
Zn/Pb	377.00	277.28	208.18	199.94
Ca/Mg	13.33	9.04	9.66	13.55

For the check-up our laboratory data the certified reference material of human hair GBW09101, obtained from Shanghai Institute of Nuclear Research, was used.

Results

Analysis of the data obtained from women with newly detected breast cancer (T1N0M0) showed significant decrease in concentration of some heavy metals and toxic elements such as As, Cd, Ni, Pb, and lower level of Cu as compared with the control group (Table 1). Decrease of As/Se and Cd/Se rates ($P<0.05$) was also found in the group I (Table 2).

Further progression of the tumor process (increase of tumor in size, involvement of regional lymph nodes, appearance of metastases, tumor disintegration) resulted in significant decrease of Zn level in hair of patients in comparison with the control. As in the group I, in the group II the tendency toward decrease of toxic elements was detected, however the changes was significant only for vanadium. It was an interesting fact that decrease of hair Si level ($P<0.05$) was observed in the group II as compared to the control. Study of changes in major and trace elements status of breast cancer sufferers depending on stage of the process unveiled no significant difference between the two groups.

Changes in mineral metabolism of persons after mastectomy (2–7 years after the operation) complied the following principles. In comparison with healthy persons of the same age group, operated patients have significantly decreased level of Se in hair and a tendency to Zn deficiency, which is more or less observed in all groups of patients. Concentration of hair As, Cd, Ni, Pb, Si and Cu in women of the group III do not differ from the control. The exception is Sn, Ti and V. Thus, tendency to decrease of hair Sn and V, appeared in the groups I and II, still persists in several years after the disease, significantly distinguishing the patients from healthy persons. However, concentration of titanium in hair of women of the group III is significantly higher than control ($P<0.05$). When compared with the control, change of Ca/Mg ratio was also found in the group III. Analysis of relative occurrence of major and trace element deficiencies/excesses showed that number of persons with Zn deficiency (lower than 130 mg/kg of hair) increased in breast cancer sufferers in comparison with healthy group (Table 3). The highest occurrence of Zn deficiency was observed in group of women, going through mastectomy. Analogous picture was observed for Se, where occurrence of low concentrations (lower than 0.35 mk/kg of hair) is maximally pronounced in the group III. Dynamics of changes in relative number of persons with clear Cu deficiency (less than 9.5 mg/kg of hair) indicates that development of tumor process leads to significant increase in number of persons with Cu deficiency, with the deficiency retaining through 2–7 years after operation (11.76% in the group III vs. 2.63% in control).

Discussion

Comparison of healthy women with those suffered from breast cancer showed certain differences in concentration of major and trace elements in their hair. Thus, development of tumor process corresponds to decrease in level of toxic elements (As, Cd, Pb, Ni, V) in hair. This effect may be caused by increased utilization of these elements by tumor, that is seemingly due to its participation in metabolic reactions going in

Table 2. Significant differences in concentration of chemical elements in women's hair ($p < 0.05$).

Elements	Groups					
	I vs. II	I vs. III	II vs. III	I vs. IV	II vs. IV	III vs. IV
As				■	■	
Cd				■		
Ni		■		■		
Pb				■		
Se			■			■
Si					■	
Sn			■			■
Ti						■
V					■	■
Zn					■	
As/Se				■	■	
Cd/Se				■		
Ca/Mg		■				■

Table 3. Occurrence of imbalances in concentration of chemical elements in women's hair.

Group	Element	Upper limit	Lower limit	Normal	Increased	Decreased	Group	Element	Upper limit	Lower limit	Normal	Increased	Decreased
I	Al	0.00%	0.00%	84.62%	15.38%	0.00%	III	Al	0.00%	5.88%	88.24%	5.88%	0.00%
	As	0.00%	0.00%	100.00%	0.00%	0.00%		As	0.00%	0.00%	100.00%	0.00%	0.00%
	Be	0.00%	0.00%	100.00%	0.00%	0.00%		Be	0.00%	0.00%	100.00%	0.00%	0.00%
	Ca	7.69%	0.00%	69.23%	15.38%	7.69%		Ca	0.00%	17.65%	64.71%	17.65%	0.00%
	Cd	0.00%	0.00%	100.00%	0.00%	0.00%		Cd	0.00%	0.00%	94.12%	5.88%	0.00%
	Co	0.00%	0.00%	84.62%	0.00%	15.38%		Co	0.00%	0.00%	82.35%	0.00%	17.65%
	Cr	0.00%	7.69%	61.54%	0.00%	30.77%		Cr	0.00%	23.53%	35.29%	17.65%	23.53%
	Cu	0.00%	7.69%	76.92%	7.69%	7.69%		Cu	0.00%	5.88%	82.35%	5.88%	5.88%
	Fe	0.00%	7.69%	61.54%	0.00%	30.77%		Fe	0.00%	5.88%	70.59%	5.88%	17.65%
	Hg	0.00%	0.00%	100.00%	0.00%	0.00%		Hg	0.00%	0.00%	100.00%	0.00%	0.00%
	K	0.00%	7.69%	30.77%	38.46%	23.08%		K	0.00%	11.76%	29.41%	35.29%	23.53%
	Li	0.00%	0.00%	100.00%	0.00%	0.00%		Li	0.00%	0.00%	100.00%	0.00%	0.00%
	Mg	0.00%	23.08%	46.15%	7.69%	23.08%		Mg	5.88%	5.88%	76.47%	11.76%	0.00%
	Mn	0.00%	15.38%	69.23%	7.69%	7.69%		Mn	0.00%	0.00%	58.82%	11.76%	29.41%
	Na	0.00%	0.00%	53.85%	23.08%	23.08%		Na	0.00%	0.00%	52.94%	29.41%	17.65%
	Ni	0.00%	0.00%	100.00%	0.00%	0.00%		Ni	0.00%	0.00%	94.12%	5.88%	0.00%
	P	0.00%	0.00%	92.31%	7.69%	0.00%		P	0.00%	11.76%	76.47%	0.00%	11.76%
	Pb	0.00%	0.00%	100.00%	0.00%	0.00%		Pb	0.00%	0.00%	100.00%	0.00%	0.00%
	Se	0.00%	0.00%	76.92%	15.38%	7.69%		Se	0.00%	11.76%	29.41%	0.00%	58.82%
	Si	0.00%	0.00%	61.54%	15.38%	23.08%		Si	0.00%	5.88%	76.47%	11.76%	5.88%
	Sn	0.00%	0.00%	91.67%	8.33%	0.00%		Sn	0.00%	0.00%	100.00%	0.00%	0.00%
	Ti	0.00%	0.00%	100.00%	0.00%	0.00%		Ti	0.00%	0.00%	100.00%	0.00%	0.00%
	V	0.00%	0.00%	100.00%	0.00%	0.00%		V	0.00%	0.00%	100.00%	0.00%	0.00%
	Zn	0.00%	0.00%	76.92%	7.69%	15.38%		Zn	0.00%	11.76%	58.82%	5.88%	23.53%
II	Al	9.09%	0.00%	90.91%	0.00%	0.00%	Control	Al	0.00%	0.00%	92.11%	7.89%	0.00%
	As	0.00%	0.00%	100.00%	0.00%	0.00%		As	0.00%	0.00%	97.37%	2.63%	0.00%
	Be	0.00%	0.00%	100.00%	0.00%	0.00%		Be	0.00%	0.00%	100.00%	0.00%	0.00%
	Ca	0.00%	0.00%	63.64%	27.27%	9.09%		Ca	0.00%	5.26%	68.42%	23.68%	2.63%
	Cd	0.00%	0.00%	100.00%	0.00%	0.00%		Cd	2.63%	0.00%	94.74%	2.63%	0.00%
	Co	0.00%	0.00%	100.00%	0.00%	0.00%		Co	0.00%	0.00%	100.00%	0.00%	0.00%
	Cr	9.09%	0.00%	54.55%	9.09%	27.27%		Cr	2.63%	10.53%	50.00%	5.26%	31.58%
	Cu	0.00%	0.00%	72.73%	9.09%	18.18%		Cu	2.63%	0.00%	81.58%	13.16%	2.63%
	Fe	0.00%	36.36%	54.55%	0.00%	9.09%		Fe	0.00%	2.63%	73.68%	7.89%	15.79%
	Hg	0.00%	0.00%	100.00%	0.00%	0.00%		Hg	0.00%	0.00%	100.00%	0.00%	0.00%
	K	0.00%	0.00%	63.64%	27.27%	9.09%		K	5.26%	5.26%	52.63%	15.79%	21.05%
	Li	0.00%	0.00%	100.00%	0.00%	0.00%		Li	0.00%	0.00%	100.00%	0.00%	0.00%
	Mg	0.00%	0.00%	54.55%	18.18%	27.27%		Mg	2.63%	7.89%	73.68%	7.89%	7.89%
	Mn	0.00%	0.00%	63.64%	9.09%	27.27%		Mn	0.00%	5.26%	68.42%	5.26%	21.05%
	Na	0.00%	0.00%	54.55%	45.45%	0.00%		Na	0.00%	0.00%	60.53%	28.95%	10.53%
	Ni	0.00%	0.00%	90.91%	9.09%	0.00%		Ni	0.00%	0.00%	94.74%	5.26%	0.00%
	P	9.09%	0.00%	72.73%	9.09%	9.09%		P	5.26%	2.63%	71.05%	15.79%	5.26%
	Pb	0.00%	0.00%	100.00%	0.00%	0.00%		Pb	0.00%	0.00%	97.37%	2.63%	0.00%
	Se	9.09%	0.00%	63.64%	18.18%	9.09%		Se	5.26%	5.26%	55.26%	5.26%	28.95%
	Si	0.00%	0.00%	63.64%	9.09%	27.27%		Si	2.63%	0.00%	57.89%	31.58%	7.89%
	Sn	0.00%	0.00%	87.50%	12.50%	0.00%		Sn	2.78%	0.00%	88.89%	8.33%	0.00%
	Ti	0.00%	0.00%	90.91%	9.09%	0.00%		Ti	0.00%	0.00%	100.00%	0.00%	0.00%
	V	0.00%	0.00%	100.00%	0.00%	0.00%		V	0.00%	0.00%	100.00%	0.00%	0.00%
	Zn	0.00%	0.00%	72.73%	0.00%	27.27%		Zn	7.89%	2.63%	73.68%	7.89%	7.89%

tumor tissue. It was also reported earlier that tumor tissues in mammary gland and ovaries accumulate toxic elements more intensively than intact tissues (Spyron, 1983; Mikhaleva et al., 2002). High metabolic activity of the tumor and direct retention of As, Cd, Ni, Pb, V by tumor cells leads to slowdown of the elements elimination from the organism, not excepting elimination through hair. An indirect confirmation of this fact is normalization of level of toxic elements in women during 2-7 years of breast cancer remission. The found decline of hair Zn and Cu level in women with breast cancer seemingly reflects immunological disturbances, caused by appearance of the tumor and its further growth (Skalny, Koudrine, 2000). Low rate of saturation of the organism with this nutrients, observed in women of postmenopausal age, also assists to development of immunodeficient conditions (Favier, 1996). Apparently, decrease of Zn, Cu level in organism of postmenopausal women should be considered as a background of breast cancer development. Growth of the tumor itself is accompanied by increase of needs in this micronutrients for cell proliferation and growth, that deepens the Zn, Cu deficiency, already incident to this age group (Rosoff, Spencer, 1965; Hoffman, 1985; Antila, 1992), and leads to redistribution of the elements in organism for the benefit of the tumor (Kok et al., 1988; Schmitt et al., 1993). There are contradictive literary data about Se level in the organism during tumor development, that may be in some measure due to phaseness of the process. The above-described investigation showed multidirectional changes in Se concentration in hair of breast cancer sufferers. At the first stage, number of patients with supernormal level of hair Se increased, while after tumor resection and 2 to 7-year remission its concentration dramatically declines and percentage of persons with low Se level reaches 70.6%. This fact can be connected with distinct oxidative stress, caused by tumor development and accompanying durable period of remission and adaptation. Unfortunately, prolonged low level of Se in the organism leads to disturbances in antioxidant defence of cells including those of immune system, being a risk factor of neoformation. Virtually, there are no literary data about participation of Sn and Ti in carcinogenesis. Changes in Sn, Ti concentration, as observed in the present investigation, are the maximal in the group III and may be considered as postcasual ones. It is known that titanium has carcinostatic properties, though the underlying mechanism is unknown (Kopf, 1981).

Thus, breast cancer is a multifactor disease, where each factor has particular significance and distinction.

Conclusions

1. The conducted investigation allows to conclude that deficiency of such micronutrients as Zn, Cu, Se can be considered as a risk factor, impairing organism's antioxidant defence in women of postmenopausal age.

2. Appearance and development of the tumor in postmenopausal period leads to biochemical and immunological disturbances, evidencing in decreased elimination of some toxic elements from the organism and its participation in further development end progression of neoplastic process.

3. Changes in elemental status, detected in postmenopausal women at breast cancer, allows to determine risk groups by corresponding metabolic parameters, that may be used in screening investigations on both individual and population level.

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