ORIGINAL ARTICLE

Comparison of 35 trace elements content in malignant breast tumors with their content in the normal female mammary gland: Original data and a mini-review

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Received: July 30, 2024 **Accepted:** September 29, 2024 **Online Published:** October 11, 2024
DOI: 10.5430/jst.v14n1p31 **URL:** https://doi.org/10.5430/jst.v14n1p31

ABSTRACT

Objective: In many countries, including Russia, breast cancer ranks first in the incidence of cancers in women. The etiology of this disease remains largely unclear, but there is evidence indicating that disturbances in the somatic homeostasis of trace elements may be involved in the process of oncogenesis. Therefore, this study was aimed at identifying changes in the content of trace elements during malignant transformation of breast tissue.

Methods: For this purpose, an effective method of small sample analysis by means of inductively coupled plasma mass spectrometry was developed. The method makes it possible to determine the content of 35 trace elements in microsamples (with mass $\geq$ 10 mg) of breast tissue obtained by puncture biopsy. With the help of this technique, the samples of cancerous (n = 43) and normal (n = 38) breast tissue were studied.

Results: In malignant breast tissue, the content of Al, As, B, Cd, Co, Cs, Cu, Mg, Mn, Mo, Ni, Rb, Se, Sr, Ti, Tl, U, V, Zn, and Zr was higher, while the content of Ge, Pb, Sb and Th was lower than in healthy gland tissue. All the identified differences were statistically significant.

Conclusions: The significant disruption of somatic homeostasis of trace elements resulting from malignant transformation of breast tissue has been described, but its cause has not been determined, so additional research is required. Further the method we employ, which we have developed and described here, requires tissue samples weighing only a few milligrams, so it is possible to use it with tissue obtained from puncture tissue biopsies.

Key Words: Breast cancer, Mammary gland of health females, Trace elements, Inductively coupled plasma mass spectrometry

1. INTRODUCTION

Despite the obvious successes in the diagnosis of breast cancer (BCa) achieved in recent decades, there are still many unresolved issues in the treatment and, especially, prevention of this disease, as a result of which BCa still remains one of the most common cancers worldwide and continues to be a leading cause of mortality throughout the world.[1] To achieve successful prevention of breast cancer and improvement in its treatment is not possible without a clear understanding of the etiology of this disease. However, until now, the etiology and pathogenesis of BCa remains largely unclear. Numerous epidemiological studies have identified a

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number of genetic and non-genetic factors associated with the risk of developing BCa.[1–4] These factors can be divided into three groups related to genetics, lifestyle (including behavior, nutrition, physical activity, type of work, bad habits, etc.) and environmental conditions. There is still ongoing controversy around many of the identified factors, but some of them have been confirmed by all studies. Among these indisputable factors are gender (in 99% of cases, BCa occurs in women) and age, since the risk of BCa increases with age, although it is noted that BCa is "getting younger" for the proportion of young women suffering from BCa is constantly increasing.

In our previous studies, we investigated age-related changes in the content of certain trace elements (TE) in the mammary gland of healthy women,[5,6] guided by the idea that age-related changes in elemental somatic homeostasis (deficiency or excess) can provoke malignant neoplasms. To carry out these studies, we have developed methods for productive analysis of small mass breast tissue samples (for example, obtained by puncture biopsy) by means of atomic emission spectrometry and mass spectrometry with inductively coupled plasma (ICP-AES and ICP-MS, respectively). These methods make it possible to quantify the content of about 50 minor and trace elements in the samples.[7–9] Disturbances of TE homeostasis leading to malignant transformation of breast tissue can be associated not only with the physiology of aging, but also with other factors - insufficient uptake of TEs into the human body, due, for example, to dietary habits, social reasons, smoking and other such bad habits, working in the presence of toxins in certain hazardous industries, the use of some cosmetics, consumption of certain food additives and medications, as well as environmental changes.[10,11]

In our previous studies, we found that malignant tumors of the bones, prostate and thyroid glands differ significantly in the content of many chemical elements, including TE, from the normal tissues from which the tumors develop.[12–39] There are several dozen studies in the scientific literature that have examined the TE content in normal and malignant breast tissues.[40–75] These studies also noted high concentrations of some TEs, especially metals, in cancerous breast tissue. Despite the relatively large number of studies of the elemental composition of normal and cancerous breast tissue, due to the wide scatter of such data, and sometimes their inconsistency, reliable information about the TE content in normal breast tissue and during its malignant transformation is still lacking.

The main goal of the study was to compare changes in the content of TEs in breast tissue during its malignant transformation with changes associated with age-related physiology. For this purpose, using the previously developed ICP-MS technique,[6,9] the content of 35 TE in tissue samples of malignant breast tumors was quantified. To compare our results with published data meaningfully, we conducted a mini review of the literature on this topic. Using the results of the review, we determined the median values for each of the 35 TEs and compared these median values with our own similar data, which measured the content of TEs in cancerous breast tissue. For those TEs for which there was good agreement with the medians of the literature data and which with a high probability could be considered close to the true values, a comparison was made of age-related changes in the TE content in breast tissue with the changes that occur during its malignancy.

2. METHODS

2.1 Tissue samples

Tumor tissue samples were collected from patients hospitalized in the thoracic department of the Medical Radiological Research Center. All patients (n = 43, age from 35 to 77 years) were Caucasian, with a Caucasian lifestyle. They had been diagnosed with breast cancer for the first time and had not yet received any treatment. Pregnant patients were excluded from the study, as well as patients with previous operations, impaired renal function, anemia, diabetes and other chronic diseases, as well as those taking micronutrient supplements (Fe, Cu, Zn, Se and others). Informed consent was obtained from all patients before breast tissue sampling. Each patient underwent a thick-needle puncture biopsy of the affected area of the mammary gland for morphological examination and assessment of its TE content. For those cancer patients, who received surgical treatment, samples of resected material were also used for both morphological examination and TE analysis. In all cases, the diagnosis was confirmed by clinical and morphological results.

Randomized samples of normal breast tissue were obtained from autopsies of 38 women (ages 16 to 60 years) who had died suddenly. An autopsy was performed in the forensic medical examination department of the Obninsk City Hospital on the first day after the sudden death. The typical causes of death for most of these women were automobile accidents and injuries. Available clinical data were reviewed for each victim. None of them had a history of intersex diseases, endocrine diseases, neoplasms or other chronic diseases that would interfere with normal breast development. None of the subjects received drugs that affected the morphology of the mammary gland and/or the content of TE in the gland. Morphologically, each breast tissue sample taken corresponded to the age norm. After weighing the samples intended for elemental analysis, they were lyophilized and

homogenized.[76]

All studies were approved by the Ethical Committees of the Medical Radiological Research Centre, Obninsk. All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments, or with comparable ethical standards.

2.1.1 *Sample preparation and ICP-MS measurements*

Deionized water was distilled without boiling in a PTFE Subboiler ECO IR Maassen "Water and acid purification system" (Germany) and nitric acid for analysis (65%, max 0.005 ppm Hg) from Merck (Germany) were used for sample preparation and element analysis. A solution of nitric acid (2%) was prepared by dilution of this Merck nitric acid with the deionized water and then used to prepare the solutions to be analyzed. A technique for microwave autoclave acid digestion of small mass (a few dozen mg) samples of the breast tissue samples had been developed earlier[7] and it was applied in the current study.

An X Series II inductively coupled plasma quadrupole mass spectrometer (ICP-MS) made by Thermo Scientific equipped with a concentric atomizer and a quartz cyclone atomization chamber cooled (up to 2°C) by a Peltier element was used. To calibrate the spectrometer reference solutions of elements obtained from High-Purity Standards (North Charleston, SC, USA) were used. Among them are CRM-TMDW (26 trace metals in drinking water), ICP-MS-68A (68 elements containing in solutions A and B) and single-element solutions (B, Mg, Al, Mn, Ni, Cu, Zn, Se, Rb, Sr, Cs, Ba). The parameters of the measurement procedure were as follows: generator output power 1,400 W, plasma-forming gas (argon) consumption 13 L/min, auxiliary gas consumption 1.25 L/min, argon flow rate through the atomizer 0.88 L/min, plasma sampling depth 105 rel. units and sample flow rate 1 mL/min. Mass spectra were measured using two scanning modes: panoramic (Survey Scan) with 5 passes from 5 to 244 m/z and at points (Peak Jumping) with 1 channel per weight, the integration time of 20 ms, and with 25 passes. Subject to all the device settings, the level of oxide ions CeO+/Ce+ is no more than 2%, and the level of doubly charged ions (Ba2+/Ba+) is no more than 3%. To correct the possible registration efficiency drift indium is used as an internal standard.

All measurements were performed using PlasmaScreen software. The ICP–MS data were processed using the iPlasmaProQuad software developed at our laboratory.[77] This program was designed to facilitate comprehensive processing of the information obtained from a mass spectrometer. The program involves all stages of processing beginning with, calibration then proceeding to calculation of element concentrations, estimation of measurement uncertainty, introducing a set of various corrections, testing the quality of the results, etc. The program outputs the multidimensional arrays of results, so allowing their reliable interpretation.

2.1.2 *Systematic mini review*

A systematic search was conducted using databases such as PubMed, Web of Science, Scopus and Google Scholar to identify literature published up to June 2024 for the TE under consideration (Al, As, B, Ba, Bi, Cd, Ce, Co, Cr, Cs, Cu, Ga, Ge, La, Li, Mg, Mn, Mo, Nb, Nd, Ni, Pb, Rb, Sb, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Zn, and Zr) in normal and malignant breast tissue. Key search terms used in the search strategy included "trace elements" in combination with "breast," "breast cancer," "breast tumor," "breast carcinoma," or "cancer of mammary gland." Additionally, we searched all results presented in previous reviews and relevant meta-analyses of our topic of interest.

Studies were included only if they met the following criteria: (1) only human participants; (2) quantitative data on the TE of interest were presented; (3) control groups used breast tissue samples from healthy women; (4) in patients suffering from breast cancer, the diagnosis was confirmed morphologically. In some cases, review articles were included in our study if they were relevant to the topic and met the above requirements, but the focus was on original work. There were no restrictions on the language of published works.

Subsequently, literature data were collected and classified for each TE depending on the condition of the breast tissue (normal or cancerous). Among the published data on the mean values of a particular TE, the median of the collected mean values for healthy and tumor breast tissue was determined.

2.2 Statistics

Using MS Excel programs, the main statistical parameters such as arithmetic mean, standard deviation, standard error of the mean, minimum and maximum values, median, percentiles with levels of 0.025 and 0.975 were calculated for the mass fractions (mg/kg dry tissue) of each TE. The significance of the difference in results between the two groups (normal and cancerous breast tissue) was assessed using the parametric Student's *t*-test and the non-parametric Wilcoxon-Mann-Whitney *U*-test. MS Excel was also used to determine the median values of the mean contents of Al, As, B, Ba, Bi, Cd, Ce, Co, Cr, Cs, Cu, Ga, Ge, La, Li, Mg, Mn, Mo, Nb, Nd, Ni, Pb, Rb, Sb, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Zn, and Zr in normal and malignant breasts tissues found in published articles.

3. RESULTS

Data on the mass fraction of the TEs (Al, As, B, Ba, Bi, Cd, Ce, Co, Cr, Cs, Cu, Ga, Ge, La, Li, Mg, Mn, Mo, Nb, Nd, Ni, Pb, Rb, Sb, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Zn, and Zr) in normal and cancerous breast tissue, obtained using the method we developed, are presented in Tables 1 and 2, respectively. The table contains the values of the arithmetic mean, standard deviation, standard error of the mean, minimum and maximum values, median, percentiles with levels of 0.025 and 0.975.

Table 1. Basic statistical parameters of 35 trace elements mass fraction (mg/kg dry tissue) in normal female breast tissue

Element	DL	M(M_{max})	SD	SEM	Min	Max	Med.	P0.025	P0.975
Al	0.5	3.4	2,0	0.4	1.2	7.4	2.6	1.2	7.2
As	0.01	0.030	0.015	0.003	0.01	0.064	0.026	0.0095	0.0585
B	0.05	0.17	0.084	0.021	0.068	0.38	0.167	0.068	0.35
Ba	0.02	0.17	0.148	0.031	0.027	0.60	0.140	0.031	0.57
Bi	0.001	0.014	0.018	0.005	0.0010	0.062	0.0072	0.0013	0.056
Cd	0.002	0.047	0.033	0.006	0.0102	0.13	0.037	0.012	0.12
Ce	0.001	0.0066	0.0038	0.0008	0.0018	0.016	0.0058	0.0020	0.015
Co	0.007	(0.007)	-	-	< 0.007*	0.020	-	-	-
Cr	0.02	0.29	0.157	0.027	0.042	0.66	0.28	0.065	0.63
Cs	0.004	(0.004)	-	-	< 0.004*	0.073	-	-	-
Cu	0.02	0.87	0.544	0.095	0.30	2.6	0.73	0.32	2.24
Ga	0.005	(0.0053)	-	-	< 0.005*	0.016	-	-	-
Ge	0.0005	(0.0055)	-	-	< 0.0005*	0.022	-	-	-
La	0.001	0.0062	0.0047	0.0010	0.0016	0.024	0.0048	0.0017	0.017
Li	0.005	0.012	0.005	0.0015	0.006	0.019	0.012	0.006	0.019
Mg	0.05	20.8	13.0	2.3	10	79	18	10.0	44.9
Mn	0.02	0.13	0.14	0.025	0.042	0.77	0.092	0.043	0.50
Mo	0.009	(0.0091)	-	-	< 0.009*	0.025	-	-	-
Nb	0.001	0.012	0.014	0.004	0.0033	0.055	0.0071	0.0033	0.044
Nd	0.001	(0.0013)	-	-	< 0.001*	0.0130	-	-	-
Ni	0.02	0.14	0.087	0.015	0.027	0.32	0.11	0.032	0.31
Pb	0.005	2.2	2.7	0.50	0.20	13.0	1.1	0.24	9.2
Rb	0.005	0.37	0.36	0.063	0.092	1.7	0.25	0.096	1.4
Sb	0.001	0.0344	0.0357	0.0069	0.0090	0.145	0.0180	0.00965	0.131
Se	0.1	-	-	-	< 0.1*	-	-	-	-
Sn	0.01	0.11	0.11	0.023	0.035	0.56	0.068	0.036	0.38
Sr	0.005	0.52	0.38	0.065	0.055	1.9	0.46	0.095	1.5
Th	0.0001	(0.005)	-	-	< 0.0001*	0.0060	-	-	-
Ti**	0.001	0.83	0.59	0.16	0.19	1.9	0.66	0.21	1.9
Tl	0.0001	-	-	-	< 0.0001*	-	-	-	-
U	0.0001	-	-	-	< 0.0001*	-	-	-	-
V	0.01	(0.012)	-	-	< 0.01*	0.060	-	-	-
W	0.002	0.080	0.104	0.030	0.0020	0.335	0.031	0.00384	0.298
Zn	0.05	4.0	2.9	0.50	1.6	15	3.	1.6	13
Zr	0.01	-	-	-	< 0.01*	-	-	-	-

Note. DL: Detection limit, M_{max}: Arithmetic mean (see Eq.1), SD: Standard deviation, SEM: Standard error of mean, Min: Minimum value, Max: maximum value, Med.: Median, P0.025: Percentile with 0.025 level, P0.975: Percentile with 0.975 level, *Below Detection Limit, **A scalpel made of ultra-pure Ti was used for sampling

Table 3 depicts differences between the mean values of mass fractions of the studied TE in normal and cancerous breast tissue evaluated by the parametric Student's *t*-test and the nonparametric Wilcoxon-Mann-Whitney *U*-test.

Comparison of our results with literature data for the mass fractions of Al, As, B, Ba, Bi, Cd, Ce, Co, Cr, Cs, Cu, Ga, Ge, La, Li, Mg, Mn, Mo, Nb, Nd, Ni, Pb, Rb, Sb, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Zn, and Zr in normal and cancerous breast tissue is shown in Tables 4 and 5, respectively. Column 2 of these tables present the median of the published mean values for each TE, and in parentheses the number of studies that contained the quantitative data on the content of this TE in normal and/or cancerous breast tissue is indicated. Columns 3 and 4 indicate, respectively, the minimum and maximum values (arithmetic mean $\pm$ standard deviation or median) of the mass fraction of each TE found in the reported data; the number of samples studied is indicated in parentheses and the corresponding link is given in square brackets.

Table 2. Basic statistical parameters of 35 trace elements mass fraction (mg/kg dry tissue) in the cancerous breast tissue of females

Element	M (M_{max})	SD	SEM	Min	Max	Med.	P0.025	P0.975
Al	8.9	12.	1.8	0.5	69	4.6	1.0	30.8
As	0.036	0.018	0.003	0.010	0.11	0.030	0.016	0.060
B	0.37	0.15	0.023	0.19	0.83	0.32	0.21	0.696
Ba	0.37	0.95	0.14	0.050	6.1	0.17	0.060	2.03
Bi	0.062	0.20	0.030	0.002	0.86	0.007	0.001	0.783
Cd	0.17	0.13	0.020	0.013	0.67	0.14	0.027	0.439
Ce	0.033	0.15	0.023	0.001	1.0	0.007	0.001	0.070
Co	0.011	0.0088	0.0013	0.0030	0.055	0.010	0.0040	0.0295
Cr	0.50	1.4	0.22	0.12	9.4	0.24	0.14	1.48
Cs	0.013	0.0098	0.0015	0.0030	0.041	0.011	0.0030	0.0388
Cu	3.7	2.6	0.40	1.5	14	3.0	1.6	11.9
Ga	0.0063	0.0037	0.0006	0.0010	0.016	0.0060	0.0011	0.014
Ge	0.0025	0.0018	0.0003	0.0005	0.010	0.0020	0.0005	0.0060
La	0.018	0.093	0.014	0.001	0.61	0.002	0.001	0.029
Li	0.082	0.351	0.053	0.001	1.70	0.005	0.002	1.5
Mg	320	150	23	120	800	270	130	660
Mn	0.51	0.27	0.041	0.17	1.70	0.44	0.20	0.97
Mo	0.033	0.015	0.0023	0.0080	0.080	0.030	0.010	0.060
Nb	0.0082	0.031	0.0047	0.0002	0.20	0.0020	0.0003	0.036
Nd	0.0022	0.0043	0.0007	0.0001	0.020	0.0010	0.0001	0.019
Ni	0.17	0.21	0.032	0.030	1.4	0.12	0.037	0.43
Pb	0.25	0.54	0.082	0.010	2,8	0.090	0.010	1.8
Rb	6.1	4.3	0.65	1.9	25	4.6	2.1	15
Sb	0.0048	0.0047	0.0007	0.0005	0.026	0.0040	0.0010	0.018
Se	0.59	0.28	0.043	0.20	1.6	0.50	0.30	1.1
Sn	0.080	0.059	0.009	0.020	0.37	0.060	0.030	0.18
Sr	1.3	1.3	0.20	0.04	7.2	0.88	0.27	4.4
Th	0.0015	0.0015	0.00022	0.00010	0.0050	0.0010	0.00010	0.0050
Ti*	4.0	6.17	0.94	0.42	37	2.40	0.49	17
Tl	0.00091	0.00090	0.00014	0.00010	0.0040	0.0010	0.00010	0.0030
U	0.0012	0.00137	0.00021	0.00010	0.0050	0.00050	0.00010	0.0050
V	0.046	0.0247	0.0038	0.011	0.10	0.040	0.017	0.10
W	0.12	0.331	0.051	0.001	1.4	0.020	0.001	1.
Zn	35	19.1	2.9	11	120	31	13	68
Zr	0.067	0.119	0.018	0.010	0.71	0.031	0.010	0.36

Note. M_{max}: Arithmetic mean (see Eq.1), SD: Standard deviation, SEM: Standard error of mean, Min: Minimum value, Max: Maximum value, Med.: Median, P0.025: Percentile with 0.025 level, P0.975: Percentile with 0.975 level, *A scalpel made of ultra-pure Ti was used for sampling

Table 3. Comparison of mean values ($M \pm$ SEM) of trace elements mass fraction (mg/kg dry tissue) in normal (*N*) and cancerous (BCa) breast tissue

Element	Mass fraction of chemical elements in female breast tissue				Ratio BCa to N
	N (n = 38)	BCa (n = 43)	*t*-test *p*	*U*-test *p*	
Al	3.4 ± 0.4	8.9 ± 1.8	.0045*	< .01*	2.6
As	0.030 ± 0.003	0.036 ± 0.003	.019*	< .01*	1.2
B	0.17 ± 0.02	0.373 ± 0.023	< .000001*	< .01*	2.2
Ba	0.17 ± 0.03	0.37 ± 0.14	.20	> .05	2.1
Bi	0.014 ± 0.005	0.06 ± 0.03	.12	> .05	4.4
Cd	0.047 ± 0.006	0.17 ± 0.02	< .000001*	< .01*	3.6
Ce	0.0066 ± 0.0008	0.03 ± 0.02	.26	> .05	5.0
Co	0.007	0.011 ± 0.001	.0026*	< .01*	1.6
Cr	0.29 ± 0.02	0.50 ± 0.22	.33	> .05	1.74
Cs	0.004	0.013 ± 0.002	.00034*	< .01*	3.3
Cu	0.87 ± 0.09	3.7 ± 0.4	< .000001*	< .01*	4.3
Ga	0.0053	0.0063 ± 0.0006	.14	> .05	1.2
Ge	0.0055	0.0025 ± 0.0003	< .000001*	< .01*	0.45
La	0.0062 ± 0.001	0.02 ± 0.01	.39	> .05	2.9
Li	0.012 ± 0.002	0.08 ± 0.05	.19	> .05	7.0
Mg	21 ± 2	317 ± 23	< .000001*	< .01*	15
Mn	0.13 ± 0.03	0.51 ± 0.04	< .000001*	< .01*	4.0
Mo	0.0091	0.033 ± 0.002	< .000001*	< .01*	3.6
Nb	0.012 ± 0.004	0.0082 ± 0.005	.56	> .05	0.68
Nd	0.0013	0.0022 ± 0.0007	.22	> .05	1.7
Ni	0.14 ± 0.02	0.17 ± 0.03	.030*	< .05*	1.2
Pb	2.2 ± 0.5	0.25 ± 0.08	.00065*	< .01*	0.12
Rb	0.37 ± 0.06	6.1 ± 0.7	< .000001*	< .01*	17
Sb	0.034 ± 0.007	0.0048 ± 0.0007	.00021*	< .01*	0.14
Se	< 0.1	0.59 ± 0.04	< .000001*	< .01*	> 5.9
Sn	0.11 ± 0.02	0.080 ± 0.009	.21	> .05	0.71
Sr	0.52 ± 0.07	1.29 ± 0.20	.00036*	< .01*	2.5
Th	0.005	0.0015 ± 0.0002	< .000001*	< .01*	0.30
Ti**	0.83 ± 0.16	4.0 ± 0.9	.0013*	< .01*	4.9
Tl	< 0.0001	0.0009 ± 0.0001	< .000001*	< .01*	> 9.1
U	< 0.0001	0.0012 ± 0.0002	.000004*	< .01*	> 12
V	0.012	0.046 ± 0.004	< .000001*	< .01*	3.9
W	0.08 ± 0.03	0.12 ± 0.05	.54	> .05	1.5
Zn	4.0 ± 0.5	35 ± 3	< .000001*	< .01*	8.9
Zr	< 0.01	0.067 ± 0.02	.0029*	< .01*	> 6.7

Note. M: Arithmetic mean, SEM: Standard error of mean, *t*-test: Student's *t*-test, *U*-test: Wilcoxon-Mann-Whitney *U*-test, *Significant values, **A scalpel made of ultra-pure Ti was used for sampling

Table 4. Median, minimum and maximum value of means of chemical element mass fractions (mg/kg dry tissue) in normal breast tissue of females according to data from the literature in comparison with the results of this work

Element	Published data [Reference]		The results of this work	
	Median of means (n)*	Minimum of means M or M ± SD, (n)**	Maximum of means M or M ± SD, (n)**	M ± SD n = 44
Al	3.5 (4)	0.103 (52) [40]	38.4 (20) [41]	3.4 ± 2.0
As	0.48 (3)	0.095 (3) [42]	< 5 (-) [43]	0.030 ± 0.015
B	< 0.16 (1)	< 0.16 (-) [43]	< 0.16 (-) [43]	0.17 ± 0.08
Ba	3.1 (2)	0.030 (-) [43]	6.24 ± 0.59 (-) [44]	0.17 ± 0.15
Bi	<0.06 (1)	< 0.06 (-) [43]	< 0.06 (-) [43]	0.014 ± 0.018
Cd	0.034 (5)	0.0310 (8) [45]	< 0.4 (-) [43]	0.047 ± 0.033
Ce	0.0012 (1)	0.0012 (1) [46]	0.0012 (1) [46]	0.0066 ± 0.0038
Co	< 0.04 (3)	0.0360 ± 0.0008 (18) [47]	0.06 (20) [41]	0.007
Cr	0.088 (7)	0.0012 (1) [46]	2.44 ± 0.23 (-) [44]	0.28 ± 0.16
Cs	0.0008 (1)	0.0008 (1) [46]	0.0008 (1) [46]	0.004
Cu	2.56 (19)	0.4 (1) [46]	2,280 ± 140 (-) [48]	0.87 ± 0.54
Ga	0.005 (2)	0.004 (1) [46]	< 0.006 (-) [43]	0.0053
Ge	0.0004 (1)	0.0004 (1) [46]	0.0004 (1) [46]	0.0055
La	< 0.6 (1)	< 0.6 (-) [43]	< 0.6 (-) [43]	0.0062 ± 0.0050
Li	-	-	-	0.012 ± 0.005
Mg	85.5 (4)	4.5 ± 0.9 (-) [44]	680 (4) [49]	20.8 ± 13.0
Mn	0.5 (7)	0.06 (-) [43]	3.74 (4) [49]	0.13 ± 0.13
Mo	0.22 (4)	0.008 (1) [46]	0.22 (20) [41]	0.0091
Nb	< 0.3 (2)	0.0004 (1) [46]	< 0.6 (-) [43]	0.012 ± 0.012
Nd	-	-	-	0.0013
Ni	0.16 (7)	0.01 (1) [46]	1.14 (20) [41]	0.14 ± 0.09
Pb	0.128 (6)	0.0081 (1) [46]	3.21 ± 2.15 (16) [44]	2.2 ± 2.2
Rb	626 (2)	0.2 (1) [46]	2,504 (4) [49]	0.37 ± 0.36
Sb	0.044 (2)	0.030-0.044 (2) [42]	5.0 (-) [43]	0.034 ± 0.034
Se	0.22 (5)	0.062 ± 0.016 (6) [50]	1.42 (8) [51]	< 0.1
Sn	0.52 (1)	0.52 (-) [43]	0.52 (-) [43]	0.11 ± 0.11
Sr	0.2 (4)	0.12 (-) [43]	0.70 ± 0.22 (16) [44]	0.52 ± 0.40
Th	-	-	-	0.0050
Ti	0.13 (2)	< 0.1 (-) [43]	0.16 (1) [46]	0.83 ± 0.60
Tl	0.006 (3)	0.0006 (1) [52]	< 0.08 (-) [43]	< 0.0001
U	< 0.002 (3)	0.0004 (1) [46]	0.0060 ± 0.0006 (3) [53]	< 0.0001
V	< 0.008 (1)	< 0.008 (-) [43]	< 0.008 (-) [43]	0.012
W	-	-	-	0.080
Zn	8.3 (17)	2.88 (46) [54]	27.8 ± 5.0 (20) [55]	4.0 ± 3.0
Zr	< 0.42 (2)	0.032 (8) [56]	< 0.8 (-) [43]	< 0.01

Note. M: arithmetic mean, SD – standard deviation, (n)*: number of all references; (n)**: Number of samples

4. DISCUSSION

The results obtained are considered reliable, since to control their reliability, the TE content in the international certified reference materials MODAS-5 (Cod tissue), MODAS-3 (Herring tissue) and IAEA-153 (Milk powder) was determined using the ICP-MS method that we developed. A previous comparison of the results obtained with the certificate data provided for these standards for all the determined TEs (Al, As, B, Ba, Bi, Cd, Ce, Co, Cr, Cs, Cu, Ga, Ge, La, Li, Mg, Mn, Mo, Nb, Nd, Ni, Pb, Rb, Sb, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Zn, and Zr) showed good agreement.[6, 7, 9]

Table 5. Median, minimum and maximum value of means of chemical element mass fractions (mg/kg dry tissue) in cancerous breast tissue of females according to data from the literature in comparison with results of this work

Element	Published data [Reference]			This work's results
	Median of means (n)*	Minimum of means M or M ± SD, (n)**	Maximum of means M or M ± SD, (n)**	M ± SD n = 44
Al	14.4 (21)	0.157 (100) [40]	564 ± 41 (10) [57]	8.9 ± 11.9
As	0.077 (9)	0.0048 (63) [58]	4.12 ± 1.64 (18) [59]	0.036 ± 0.018
B	-	-	-	0.37 ± 0.15
Ba	10.2 (2)	0.13 (17) [60]	20.2 ± 4.4 (-) [44]	0.37 ± 0.95
Bi	-	-	-	0.062 ± 0.200
Cd	0.375 (16)	0.0042 (63) [58]	363 ± 935 (7) [61]	0.17 ± 0.13
Ce	-	-	-	0.033 ± 0.150
Co	0.21 (16)	0.0049 ± 0.0019 (6) [62]	9.1 ± 16.2 (53) [63]	0.011 ± 0.009
Cr	1.24 (21)	0.066 (63) [58]	55 ± 15 (-) [44]	0.5 ± 1.4
Cs	0.018 (9)	0.014 (46) [64]	3.2 ± 1.4 d (6) [65]	0.013 ± 0.010
Cu	6.12 (43)	0.00062 ± 0.00006 (-) [66]	1,231 ± 154 (-) [48]	3.7 ± 2.6
Ga	2.8 (1)	2.8 (1) [65]	2.8 (1) [65]	0.0063 ± 0.0037
Ge	0.64 (1)	0.64 ± 0.38 (26) [67]	0.64 ± 0.38 (26) [67]	0.0025 ± 0.0018
La	5 (1)	5 (6) [68]	5 (6) [68]	0.018 ± 0.093
Li	2.35 (1)	2.35 ± 3.96 (53) [63]	2.35 ± 3.96 (53) [63]	0.082 ± 0.350
Mg	305 (17)	3 (6) [68]	1,400 ± 400 (6) [65]	320 ± 150
Mn	1.42 (20)	0.026 (17) [60]	17.3 ± 4.9 (18) [59]	0.51 ± 0.27
Mo	2.45 (4)	1.00 (19) [41]	6.16 ± 5.42 (53) [63]	0.033 ± 0.015
Nb	-	-	-	0.0082 ± 0.0310
Nd	-	-	-	0.0022 ± 0.0043
Ni	2.54 (17)	0.1 (12) [69]	8.57 ± 2.24 (18) [59]	0.17 ± 0.21
Pb	1.55 (17)	0.05 (63) [58]	31.7 ± 50.8 (53) [63]	0.25 ± 0.54
Rb	13 (19)	0.75 ± 0.12 (26) [70]	28.5 (-) [71]	6.1 ± 4.3
Sb	0.0068 (5)	0.00035 ± 0.00019 (6) [62]	18.3 ± 12.8 (53) [63]	0.0048 ± 0.0047
Se	0.915 (31)	0.22 (63) [58]	10,231 ± 808 (80) [72]	0.59 ± 0.28
Sn	0.044 (3)	0.022 (12) [69]	0.26 (17) [60]	0.080 ± 0.059
Sr	2.24 (12)	0.07 (17) [60]	34.6 ± 11.9 (16) [73]	1.3 ± 1.3
Th	-	-	-	0.0015 ± 0.0015
Ti	13.0 (4)	1.0 (17) [60]	20.4 ± 13.1 (16) [73]	4.0 ± 6.2
Tl	-	-	-	0.00091 ± 0.00090
U	0.019 (1)	0.019 ± 0.002 (6) [53]	0.019 ± 0.002 (6) [53]	0.0012 ± 0.0014
V	1.34 (3)	1.34 ± 0.76 (25) [74]	2.0 (6) [68]	0.046 ± 0.025
W	-	-	-	0.12 ± 0.33
Zn	49.6 (53)	0.25 (63) [58]	1,158 ± 15 (-) [75]	35 ± 19
Zr	10 (1)	10 ± 5 (19) [57]	10 ± 5 (19) [57]	0.067 ± 0.119

Note. M: Arithmetic mean, SD: Standard deviation, (n)*: Number of all references; (n)**: Number of samples

The content of Tl, U and Zr in all samples of normal breast tissue was below the detection limit (DL) The Co, Cs, Ga, Ge, Mo, Nd, Th, and V mass fractions in normal breast tissue were determined in a few samples (see Table 1). The possible upper limit of the mean (Mmax) for these TE was calculated as the average mass fraction, using the value of the DL instead of the individual value when the latter was found to be below the DL (see Equation 1):

$$M_{max} = (\sum_{i}^{n_i} C_i + DL \times n_j)/n \quad (1)$$

where C_i is the individual value of the TE mass fraction in sample *i*, n_i is the number of samples with mass fraction higher than the DL, n_j is number of samples with mass fraction lower than the DL, and $n = n_i + n_j$ is number of samples that were investigated. The content of the remaining TEs analyzed (Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mg, Mn, Nb, Ni, Pb, Rb, Sb, Se, Sn, Sr, Ti, W, and Zn) was determined in all or most samples of normal breast tissue. This made it possible to calculate all the main statistical characteristics (arithmetic mean, standard deviation, standard error of the mean, minimum and maximum values, median, percentiles with levels of 0.025 and 0.975) for the mass fractions of these TEs (see Table 1).

In contrast to normal breast tissue, for cancerous tissue all the main statistical characteristics of the mass fractions of all 35 studied TEs were determined, since in all or most part of the tissue samples with malignant transformation it was possible to determine all TEs, including Co, Cs, Ga, Ge, Mo, Nd, Th, Tl, U, V, and Zr (see Table 2).

When comparing the TE content in normal and cancerous breast tissue, the statistical characteristics M, SD and SEM can only be used if the results of determining the TE content in the studied groups of samples have a normal distribution. For example, using a Student's t test for comparison requires prior evidence of a normal distribution of results within each of the two groups of samples studied (normal and cancerous). In the present study, due to the relatively small number of samples in both groups (normal group n = 38 and cancer group n = 43), such evidence was not possible, since existing criteria for determining the type of distribution of results require a larger sample size, usually several hundreds. In the work presented here, due to the small sample sizes, it was not possible to prove or disprove the "normality" of the distribution of results. Therefore, in addition to the values of *M*, SD and SEM, such statistical characteristics as median, range (minimum-maximum) and percentiles with level 0.025 and 0.0975, the use of which is possible with any type of distribution, is given for the results of TE content in breast tissue.

As follows from the data presented in Table 3, during malignant transformation of breast tissue, significant changes in the content of TE occur. In cancerous tissue, the mass fractions of all studied TEs, except for Ge, Nb, Pb, Sb, Sb, and Th, were higher than the levels in normal tissue. At the same time, the increases identified were statistically significant only for Al, As, B, Cd, Co, Cs, Cu, Mg, Mn, Mo, Ni, Rb, Se, Sr, Ti, Tl, U, V, Zn, and Zr, and the decreases were significant only for Ge, Pb, Sb, and Th, according to the parametric Student's *t*-test and the nonparametric Wilcoxon-Mann-Whitney *U*-test.

When considering the published data in Tables 4 and 5, attention is drawn to the huge difference between the minimum (Column 3) and maximum (Column 4) values, which for almost all TE amounts to two, three or more orders of magnitude. Such a wide range of published data, in our opinion, is mainly due to the insufficient attention of many authors to proper quality control of their results including sampling. The lack of proper control allows for random errors both in the direction of underestimation and in the direction of overestimation of the results of the analyses. Since these errors are random in nature, as the number of observations increases, the median of accumulated data on the content of one or another TE in normal and cancerous breast tissue should approach the true value. This interpretation of the existing spread of accumulated data allows us to compare our results (Column 5) with the medians of published mean mass fractions (Column 2) for each TE.

Table 4 reflects the results of our analytical review of literature data on the content of Al, As, B, Ba, Bi, Cd, Ce, Co, Cr, Cs, Cu, Ga, Ge, La, Li, Mg, Mn, Mo, Nb, Nd , Ni, Pb, Rb, Sb, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Zn, and Zr in the normal mammary gland: Very often, when studying the content of TE in malignant breast tumors, samples of breast tissue obtained from healthy women are not used as a "normal/control group," but instead samples of visually intact tissue adjacent to the tumor. However, such a replacement is not correct. For example, we have previously shown that, in terms of the level of TE content, intact tissue adjacent to thyroid tumors is not identical to normal thyroid tissue of healthy individuals.[78,79] Therefore, in our review of the literature, only the results obtained from the study of normal mammary glands of healthy women were used. Some values of mass fractions of TE in published articles were not expressed in terms of dry tissue. In such cases, we recalculated these values using the literature data on water content (50%)[80] and ash (1%, in dry tissue)[60] in the mammary gland of adult women. Median

values of the literature data on TE content in breast tissue of healthy women for Al, B, Bi, Cd, Ce, Cr, Cs, Cu, Ga, La, Mg, Mn, Ni, Sb, Sn, Sr, V and Zn, that we determined from our review were in relatively good agreement with the results of the present study (see Table 4). Our measurements of the mass fractions of Ba, Mo, Nb, Pb, Rb, and Se were within the range of published mean values for TE content in normal breast tissue. Our measurements of As, Co, Tl, U, and Zr were approximately an order of magnitude below survey medians and even below the lower end of the range of reported means. The result we obtained for Ge was an order of magnitude higher than in the only published study on this topic.[46] No literature data were found for Li, Nd, Th, and W (see Table 4). From our review it also follows that for many of the studied TE, the variations (Mmax/Mmin) for their content in normal breast tissue are very large and amount to several orders of magnitude (see Table 4).

The results of our analytical review of published data on the content of Al, As, B, Ba, Bi, Cd, Ce, Co, Cr, Cs, Cu, Ga, Ge, La, Li, Mg, Mn, Mo, Nb, Nd, Ni, Pb, Rb, Sb, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Zn and Zr in malignant tumors of the mammary gland are presented in Table 5. Median values of literature data on the content of TEs in cancerous breast tissue for Al, As, Cd, Cr, Cs, Cu, Mg, Mn, Rb, Sb, Se, Sn, Sr, Ti, and Zn, which we calculated using the results of the review, are in relatively good agreement with the results of our study (see Table 5). Our measurements of the mass fractions of Ba, Co, Ni, and Pb were within the published values for these TEs in cancerous breast tissue. Our measurements of the mass fractions of Ga, Ge, La, Li, Mo, U, V, and Zr were approximately one to two mathematical orders of magnitude below the medians of review results and even below the lower end of the range of published means. However, it should be noted that the published studies on the content of Ga, Ge, La, Li, Mo, U, V and Zr in malignant breast tumors, comprised only a few reports. No literature data were found on the content of B, Bi, Ce, Nb, Nd, Th, Tl, and W in malignant tumors of the breast (see Table 5). From our review it also follows that for many studied TE variations (Mmax/Mmin) their contents in cancerous breast tissue are very large and amount to several orders of magnitude (see Table 5).

Trends in changes in the TE content in malignant breast tumors compared to the norm can also be determined according to the literature data, if we use the ratio of median values of mean mass fractions for cancerous and normal tissue. The calculation of these ratios showed that during malignant transformation of breast tissue there is a multiple increase in the content of Al, Ba, Cd, Co, Cr, Cs, Cu, Ga, Ge, La, Mg, Mn, Mo, Ni, Pb, Se, Sr, Ti, U, V, Zn, and Zr (see Tables 4 and 5). Thus, both from the data obtained in our study (see Table 3) and from the literature data (see Tables 4 and 5), it follows that the content of at least such TEs as Al, Cd, Co, Cs, Cu, Mg, Mn, Mo, Ni, Se, Sr, Ti, U, V, Zn and Zr in cancerous tissue are significantly higher than in normal breast tissue.

Normally, breast tissue consists of a glandular component and stroma (adipose tissue and ligaments surrounding the ducts and lobules, blood and lymphatic vessels.[81] On average, the ratio by weight of the glandular component and adipose tissue together with stroma is approximately 1: 1.[82] It is known that the content of many TEs in adipose tissue is significantly lower than in the glandular component.[5] Tumor tissue consists predominantly of transformed glandular cells. However, even the complete absence of adipose tissue in the tumor cannot increase the mass fraction of TEs by more than a factor of two. Thus, this factor cannot explain the manifold increase in the above-mentioned TEs in cancerous tissue.

A study of the age-related dynamics of TE content in the breast tissue of healthy women revealed a significant increase in the mass fraction of As and a slight increase in the mass fractions of Cd, Nb, Pb, Sb and Sn, while the content of all other TEs decreased with age.[6] Thus, the multiple increase in the mass fraction of TEs in malignantly transformed breast tissue discovered in the present work is not a logical consequence of the normal age-related physiology of the mammary gland.

One of the possible explanations for the observed phenomenon of a multiple increase in TE content in malignant breast tumor may be associated with disturbances in the mechanisms of intracellular transport and metabolism of TEs that occur during malignancy of glandular cells. Such disturbances can lead to changes in the permeability of cell membranes and excessive accumulation of TEs in cells.

Another possible explanation may be related to the excessive intake of Al, As, B, Cd, Co, Cs, Cu, Mg, Mn, Mo, Ni, Rb, Se, Sr, Ti, Tl, U, V, Zn, and Zr into the body through food, water and inspired gases due to uncontrolled changes in the TE content of the environment. Excessive accumulation of TEs in glandular cells can lead to their malignancy. In this case, an increase in the content of many TEs should be detected not only in cancerous tissue, but also in visually intact tissue adjacent to the tumor. To confirm or refute the possibility of such a variant of breast tumorigenesis, we plan to study the TE content in samples of visually intact tissue adjacent to the breast tumors and to compare the results with the TE content levels characteristic of breast tissue of healthy women. It should also be noted that the increase in the content of some TEs in malignant breast tumors, we present here, can be

used to develop new methods for diagnosing BCa, in which TE levels will act as biomarkers. We also plan to continue research in this direction.

5. Conclusion

The ICP-MS method we have developed, makes it possible to obtain reliable data on the content of the 35 TEs: Al, As, B, Ba, Bi, Cd, Ce, Co, Cr, Cs, Cu, Ga, Ge, La, Li, Mg, Mn, Mo, Nb, Nd, Ni, Pb, Rb, Sb, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Zn, and Zr) in samples of normal and cancerous breast tissue. An important advantage of our method is its ability to determine the TE content in samples weighing only a few milligrams, which makes it possible to use it for the analysis of puncture tissue biopsy materials.

In patients with BCa, the content of Al, As, B, Cd, Co, Cs, Cu, Mg, Mn, Mo, Ni, Rb, Se, Sr, Ti, Tl, U, V, Zn and Zr in samples of malignant breast tissue was higher, and the content of Ge, Pb, Sb and Th was lower than in healthy gland tissue. All the differences identified were statistically significant. Further detailed studies are needed to understand the role of disruption of many TEs' homeostasis in malignant tissues in the etiology and pathogenesis of BCa.

Acknowledgements

The authors are extremely grateful to the late head of the thoracic department of the Medical Radiological Research Center, Prof., Dr. P.P. Firsova, and the doctor of this department, F.V. Medvedev for supplying breast samples.

Authors contributions

Vladimir Zaichick: Concept of the study, collection of breast tissue samples, freeze-drying of tissue samples, statistical processing of results, writing and translation of the article. Denis Dogadkin: Samples preparation for ICP-AES, processing and compilation of the analysis results, discussion of the manuscript text. Irina Gromyak, Dmitry Tyuri: Samples analysis by ICP-AES. Vladimir Kolotov: Development of methodology, critical analysis of the experimental data, discussion of the manuscript text.

Funding

This work was supported by the Ministry of Science and Higher Education of the Russian Federation, within the budget theme of the Vernadsky Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences.

Conflicts of Interest Disclosure

The authors declare they have no conflicts of interest.

Informed consent

Obtained.

Ethics approval

The Publication Ethics Committee of the Sciedu Press. The journal's policies adhere to the Core Practices established by the Committee on Publication Ethics (COPE).

Provenance and peer review

Not commissioned; externally double-blind peer reviewed.

Data availability statement

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

Data sharing statement

No additional data are available.

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