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Research Article

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Content of Trace Elements in Benignly Transformed and Normal Breast Tissue Determined by ICP-MS - Original Data and a Mini Review

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ABSTRACT

Background: *Many women around the world suffer from benign breast diseases. The etiology of this disease remains largely unclear, although it is known that disturbances of somatic elemental homeostasis play a certain role in breast pathology.*

Objective: *This study was aimed at identifying changes in the content of 35 trace elements during the benign transformation of breast tissue.*

Method: *For this purpose, we used the previously developed method of sample preparation, which allows determining 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 micro samples of breast tissue by using mass spectrometry with inductively coupled plasma. Using the developed technique, samples of benignly transformed and normal breast tissue were examined.*

Results: *Both from the data obtained in the present study and from our calculations made based on literature data, it was found that the content of such elements as Al, Cd, Co, Cr, Cs, Cu, Mg, Mn, Mo, Se, Sr, and Zn in benignly transformed tissue is higher than in normal breast tissue.*

Conclusions: *The detected multiple increase in the content of many trace elements in benignly transformed tissue compared to normal breast tissue can be used to develop new methods for in vitro and in vivo diagnostics, in which the trace elements levels in breast lesion will act as markers. Further deeper study and understanding of the detected phenomenon will allow the development of new methods for the prevention and treatment of benign breast diseases.*

Keywords: *benign breast diseases, trace elements, inductively coupled plasma mass spectrometry, benignly transformed breast tissue, normal breast tissue.*

Introduction

Benign breast diseases (BBD) include a wide range of clinical changes in the mammary gland [1,2]. Many women around the world suffer from BBD. For example, diseases such as fibrocystic changes occur in 50% of all women over 30 years of age, and fibroadenomas occur in 25% of women and are the most common benign tumors of the mammary gland [1]. BBD are often accompanied by malignant transformation of mammary gland tissue. For example, complex cysts carry a risk of malignancy from 23% to 31%, and papillary lesions 16% [1]. Therefore, all types of BBD are generally recognized as a risk factor for breast cancer (BC)

[3,4]. Screening tests for early detection of BC typically use full-field digital mammography and ultrasound. In complex cases, if there are doubts, histological confirmation is resorted to using percutaneous core needle biopsy. Since a biopsy is a great psychological trauma for every woman, sometimes more complex examination methods, such as contrast magnetic resonance imaging (MRI), are used before this procedure [5,6]. However, although contrast-enhanced MRI has demonstrated higher sensitivity than mammography and ultrasonography, its specificity is insufficient, leading to the problem of false-positive results - approximately 70–80% of biopsies performed after contrast MRI give a false positive result [5]. Thus, screening examinations require multiple histological confirmations, which causes a significant burden on the health care system and represents a major social problem associated with discomfort for many women. Therefore, the search for specific characteristics of benign and malignantly transformed breast tissues that could be used for differential diagnosis of these pathologies continues.

Previously, in our studies, it was shown that benign and malignantly transformed tissues of bones [7-14], prostate [15-22], and thyroid [23-33] glands differ significantly in the level of many trace elements (TEs), which made it possible to use these differences for differential diagnosis of these pathologies. These results, as well as the fact that almost 50% of benign breast disease subtypes are associated with microcalcifications [34], suggest the presence of specific levels of TEs characteristic of benignly transformed breast tissue.

Information about the TEs composition of benignly altered breast tissue is of interest not only from the point of view of searching for diagnostic indicators. It can also reflect the causes of pathology. It is known that the global spread of BBD is influenced by a complex interaction of genetic, environmental and lifestyle factors. One of the environmental factors is TEs that enter the human body with food, drinking water and air. Earlier, we paid special attention to the role of TEs in the normal physiology of the mammary gland [35,36]. In the present study, we proceeded from the fact that a violation of TEs somatic homeostasis (deficiency or excess) can provoke pathological transformation of mammary gland [37,38]. To ensure the possibility of studying not only normal tissue samples obtained during autopsy, but also pathologically altered mammary gland tissue, we developed a sample preparation technique that allows determining the content of 35 TEs in small tissue samples using inductively coupled plasma mass spectrometry (ICP-MS). This method made it possible to use tissue samples obtained using percutaneous core needle biopsy [39].

To date, several papers have been published in which the content of TEs in normal and benignly transformed breast tissue was studied using various analytical methods [40-65]. However, due to the large scatter of published quantitative data, and sometimes their inconsistency, it is not possible to draw unambiguous conclusions about the normal levels of TEs characteristic of normal breast tissue, as well as about the changes in the TEs composition occurring in BBD. Also, no systematic reviews on this topic were found in the literature that could resolve the existing contradictions and draw adequate conclusions.

The present study was aimed at comparing the content of TEs in benignly transformed breast tissue with the content of the same TEs in the breast tissue of healthy women. To determine the content of TEs, we used a previously developed technique [39]. To assess the reliability of our results, a systematic analysis of the published data on the content of TEs in benign transformed and normal breast tissue was carried out. The analysis performed allowed us to determine the median values of the data available in the literature and made it possible to compare the identified median values with our results.

Materials and Methods

Tissue samples

The study used a collection of benignly transformed breast tissue samples obtained by percutaneous core needle biopsy. The collection was collected by surgeons of the Torrocal Department of the Medical Radiological Research Center (Obninsk) in the 1990s. After biopsy, the obtained material was weighed, lyophilized [66], and weighed again. Then, each dried tissue sample was sealed in polyethylene film pre-treated with rectified ethyl alcohol, and in sealed form placed in a numbered polyethylene capsule. Samples were stored in a fume hood at room temperature. As our studies have shown, lyophilized tissue samples in this form can be stored for decades without changing the levels of TEs in them [67,68]. Eleven tissue samples were obtained from women with fibrocystic breast disease, and 6 samples represented fibroadenoma tissue. The women's age ranged from 18 to 43 years. All patients were Caucasian, with a Caucasian lifestyle.

To compare the obtained results with the levels of TEs content characteristic of the mammary glands of healthy women, randomized samples of normal mammary gland tissue were obtained during autopsy from 38 Caucasian women (aged 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 ChEs 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.

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.

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 [69] 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 1400 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 [70]. 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.

To verify the accuracy of the obtained results, Polish certified reference materials MODAS-5 (Cod tissue) and MODAS-3 (Herring tissue) and the CRM prepared by the International Atomic Energy Agency IAEA-153 (Milk powder) were used.

Systematic mini review

A systematic search was performed using PubMed, Web of Science, Scopus, and Google Scholar to identify literature published up to March 2025 on the considered 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 benignly transformed and normal breast tissue. The key terms used in the search strategy included "trace elements" or "chemical elements" in combination with "normal breast", "normal breast tissue", "health breast tissue", or "benign breast disease", "benign breast tumor", "breast fibroadenoma", and "fibrocystic breast disease". In addition, we searched for all results reported in previous reviews and relevant meta-analyses on the topic of interest.

The identified studies were included only if they met the following standards: (1) only studies involving human participants were included; (2) quantitative data on the TEs of interest were presented; (3) in patients with benign breast disease, 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 main focus was on original works. There were no restrictions on the language of published papers.

Subsequently, the literature data were collected and classified for each TE depending on the breast tissue (benignly transformed or normal). From the published data, the median of the mean values for benignly transformed and normal breast tissue was found for each specific TE.

Statistics

The main statistical parameters such as arithmetic mean, standard deviation, and standard error of the mean for mass fraction of TEs (mg/kg dry weight) were calculated using MS Excel. The significance of differences in the results between the two groups (benign transformed and normal breast tissue) was assessed using the parametric Student's t-test and the nonparametric 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 benignly transformed and normal breast tissue found in the published papers.

Results

The results of determination of mass fraction 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 three different international certified reference materials MODAS-5 (cod tissue), MODAS-3 (herring tissue) and IAEA-153 (milk powder) obtained using our developed ICP-AES method are presented in Table 1.

Figure 1 demonstrates the mean mass fraction and the range of the standard error of the mean (M±SEM) for each of the 35 studied TEs in the compared pairs - benignly transformed and normal beast tissue.

The mean values of the mass fraction and standard deviation (M±SD) of the TEs in benignly transformed beast tissue (MBT), obtained using the ICP-MS micro method developed by us, were (mg/kg dry tissue): Al 11.9±7.4, As 0.061±0.027, B 0.73±0.46, Ba 0.17±0.11, Bi 0.0105±0.0079, Cd 0.182±0.198, Ce 0.0092±0.0054, Co 0.0078±0.0043, Cr 0.38±0.20, Cs 0.0119±0.0069, Cu 3.04±1.07, Ga (0.0052), Ge (0.0057), La 0.0079±0.0079, Li 0.017±0.012, Mg 265±159, Mn 0.33±0.20, Mo 0.031±0.022, Nb 0.0051±0.0053, Nd 0.0042±0.0061, Ni 0.136±0.106, Pb 0.165±0.136, Rb 5.59±3.72, Sb 0.0032± 0.0021, Se 0.43±0.16, Sn 0.042±0.026, Sr 1.19±0.59, Th (0.0017), Ti 2.45±2.13, Tl 0.0014±0.0008, U 0.0024±0.0034, V 0.188±0.145, W 0.033±0.030, Zn 35.4±18.0, and Zr 0.016±0.012, and in the normal breast tissue (MN): Al

Table 1. ICP-MS data (Mean±SD) of trace elements mass fraction (mg kg-1, dry mass basis) in certified reference material MODAS-5 (Cod Tissue), MODAS-3 (Herring Tissue), and IAEA-153 (Powdered milk) compared to their certified values.

El	MODAS-5		MODAS-3		IAEA-153	
	Certificate	**Our result**	**Certificate**	**Our result**	**Certificate**	**Our result**
Al	-	6±1	-	14±1	-	-
As	1.64±0.27	1.7±0.1	9.24±0.81	8.8±0.4	-	-
B	-	0.34±0.05	-	9.0±0.3	-	2.03±0.07
Ba	0.162±0.028	0.18±0.02	2.71±0.28	2.6±0.1	-	0.67±0.04
Bi	0.007	0.006±0.001	-	-	-	-
Cd	0.005	0.0046±0.0004	0.33±0.03	0.32±0.01	-	-
Ce	-	0.006±0.002	-	0.021±0.008	-	-
Co	0.014	0.012±0.001	0.08±0.01	0.110±0.003	-	0.016±0.001
Cr	0.201	0.3±0.1	0.90±0.11	0.9±0.2	-	-
Cs	0.059±0.005	0.059±0.002	0.085±0.008	0.086±0.005	-	-
Cu	1.38±0.09	1.5±0.1	3.19±0.22	3.2±0.1	0.6±0.2	0.42±0.03
Ga	-	0.012±0.001	-	0.036±0.002	-	-
Ge	-	0.006±0.001	-	0.018±0.002	-	-
La	-	0.007±0.002	-	0.017±0.005	-	-
Li	0.026	0.030±0.002	0.90±0.11	0.76±0.03	-	0.034±0.005
Mg	1200±200	1178±38	3000±200	2739±75	1060±75	1023±19
Mn	0.92±0.08	0.89±0.05	5.78±0.61	5.3±0.1	-	0.22±0.04
Mo	-	-	0.13±0.02	0.14±0.01	0.3± 0.3	0.228±0.004
Nb	-	-	-	0.006±0.002	-	-
Nd	-	-	-	0.006±0.003	-	-
Ni	0.136	0.14±0.02	0.32±0.05	0.5±0.1	-	0.13±0.02
Pb	0.045	0.05±0.01	0.104±0.013	0.13±0.01	-	-
Rb	4.54±0.33	4.5±0.1	2.33±0.20	2.24±0.07	14.0±1.9	14.9±0.4
Sb	-	-	0.016±0.004	0.017±0.002	-	-
Se	1.33±0.1	1.2±0.1	2.63±0.2	2.8±0.1	-	-
Sm	-	-	0.0018	0.0015±0.0003	-	-
Sn	-	0.14±0.01	-	0.23±0.02	-	0.05±0.02
Sr	4.07±0.36	3.5±0.4	192±15	180±6	4.1±0.6	3.76±0.07
Th	-	0.002±0.001		0.003±0.001	-	0.0009±0.0008
Ti	-	<0.9	-	<2.1		<0.2
Tl	-	0.0013±0.0002	-	0.0014±0.0005	-	-
U	-	-	0.075±0.008	0.063±0.002	-	-
V	-	-	0.78±0.11	0.62±0.01	-	-
W	-	0.024±0.008	-	-	-	-
Zn	20.1±1.1	21±1	111±6	114±3	39.5±1.8	33±1
Zr	-	0.10±0.02	-	0.09±0.03	-	0.014±0.008

El – Element, Mean - arithmetical mean, SD - standard deviation

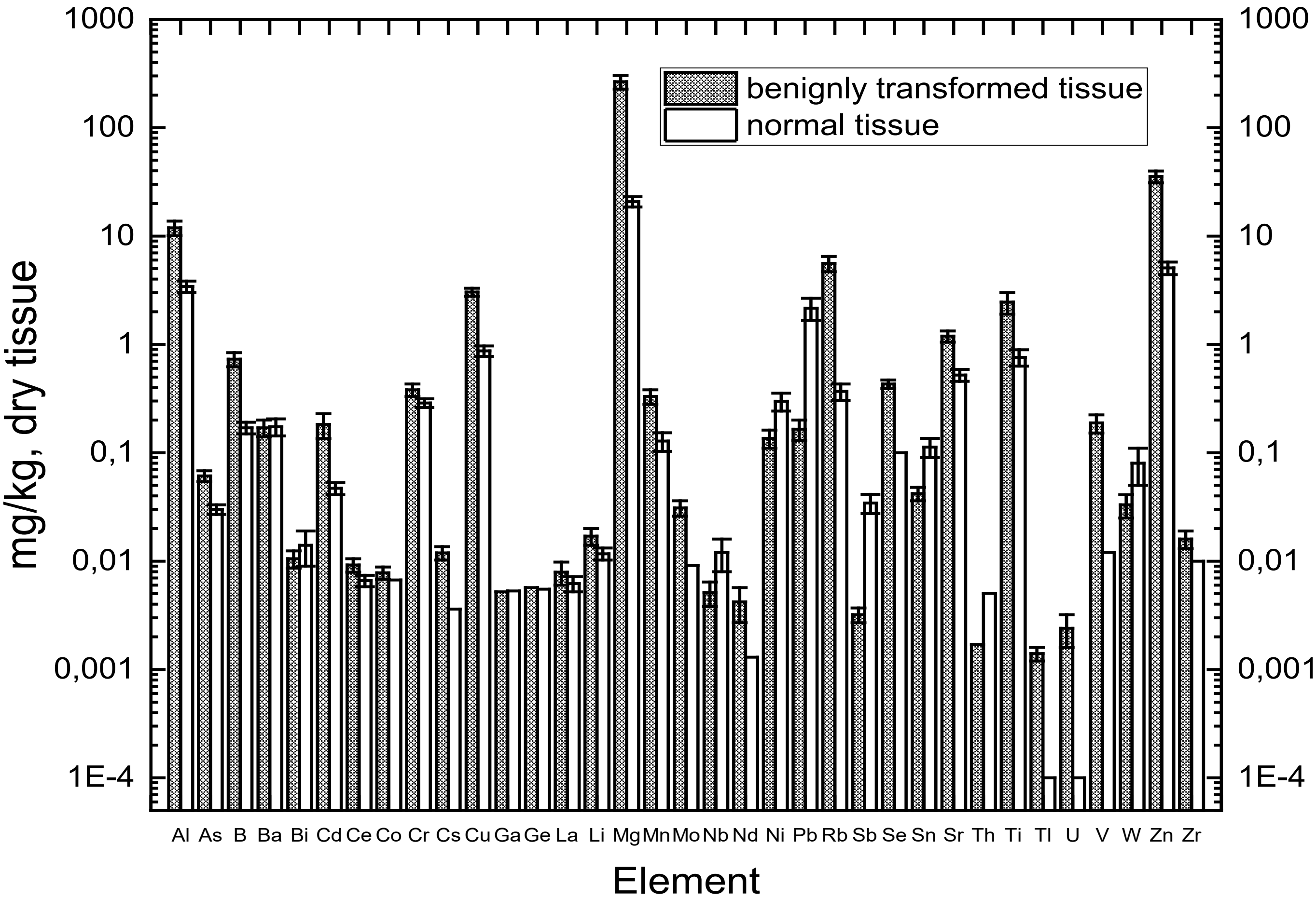

Figure 1. The mean mass fraction (M) and the range of the standard error of the mean (±SEM) for each of the 35 studied TEs in benignly transformed and normal beast tissue.

3.42±1.98, As 0.030±0.015, B 0.170±0.084, Ba 0.174±0.148, Bi 0.014±0.018, Cd 0.047±0.033, Ce 0.0066±0.0038, Co (0.0067), Cr 0.288±0.157, Cs (0.0036), Cu 0.872±0.555, Ga (0.0053), Ge (0.0055), La 0.0062±0.0047, Li 0.0117±0.0047, Mg 20.8±13.0, Mn 0.128±0.138, Mo (0.0091), Nb 0.012±0.014, Nd (0.0013), Ni 0.299±0.315, Pb 2.16±2.72, Rb 0.368±0.360, Sb 0.0344±0.0357, Se <0.1*, Sn 0.113±0.114, Sr 0.522±0.376, Th (0.00503), Ti 0.76±0.50, Tl <0.0001*, U <0.0001*, V (0.012), W 0.080±0.104, Zn 5.08±3.71, Zr <0.01* (*detection limit, in parentheses - possible upper limit of the mean).

The Ga, Ge, and Th mass fractions in benignly transformed breast tissue and Ga, Ge, Mo, Nd, and Th in normal breast tissue were determined just in few samples. The possible upper limit of the mean (M_{max}) for these TEs was calculated as the mean mass fraction, using the value of the detection limit (DL) instead of the individual value when the latter was found to be below the DL:

$$M_{max} = (\sum_{1}^{n_i} C_i + DL \times n_{j)})/n$$

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.

Figure 1 demonstrates the mean mass fraction and the range of the standard error of the mean (M±SEM) for each of the 35 studied TEs in the compared pairs - benignly transformed and normal beast tissue.

Table 2 depicts the differences between the mean values of the mass fractions of the studied TEs in the benignly transformed and normal beast tissue, assessed using the parametric Student t-test and the nonparametric Wilcoxon-Mann-Whitney U-test.

Comparison of our results with literature data for the mass fractions of TEs studied in the normal and benignly transformed beast tissue is shown in Table 3 and 4, respectively. Column 3 of these tables presents the median of the published mean values for each TE, and in parentheses the number of studies that contained quantitative data on the content of this TE in benignly transformed or normal breast tissue is indicated. Columns 4 and 5 indicate, respectively, the minimum and maximum values (arithmetic mean

Table 2. Comparison of mean values (M±SEM) of trace elements mass fraction (mg/kg dry tissue) in normal (N) and benignly transformed (BT) breast tissue of females

Element	Mass fraction of chemical elements in female breast tissue				Ratio
	N n=38	BT n=17	t-test p	U-test p	BT to N
Al	3.42±0.41	11.9±1.8	0.00019*	<0.01*	3.48
As	0.030±0.003	0.061±0.007	0.00005*	<0.01*	2.03
B	0.170±0.021	0.73±0.11	0.00011*	<0.01*	4.29
Ba	0.174±0.031	0.17±0.03	0.954	>0.05	0.98
Bi	0.014±0.005	0.0105±0.0019	0.488	>0.05	0.75
Cd	0.047±0.006	0.182±0.047	0.013*	<0.01*	3.87
Ce	0.0066±0.0008	0.0092±0.0013	0.089	>0.05	1.39
Co	0.0067	0.0078±0.0010	0.375	>0.05	>1.16
Cr	0.288±0.027	0.38±0.05	0.126	>0.05	1.32
Cs	0.0036	0.0119±0.0017	0.0036*	<0.01*	>3.51
Cu	0.87±0.10	3.04±0.26	<0.00001*	<0.01*	3.49
Ga	0.0053	0.0052	-	-	>0.98
Ge	0.0055	0.0057	-	-	>1.04
La	0.0062±0.0010	0.0079±0.0019	0.428	>0.05	1.27
Li	0.0117±0.0015	0.0170±0.0030	0.122	>0.05	1.45
Mg	20.8±2.3	265±38	<0.00001*	<0.01*	12.7
Mn	0.128±0.025	0.330±0.050	0.00095*	<0.01*	2.58
Mo	0.009	0.031±0.005	0.00078*	<0.01*	>4.44
Nb	0.012±0.004	0.005±0.001	0.106	>0.05	0.42
Nd	0.0013	0.0042±0.0015	0.075	>0.05	3.23
Ni	0.299±0.056	0.136±0.026	0.011*	<0.01*	0.45
Pb	2.16±0.50	0.165±0.035	0.00038*	<0.01*	0.08
Rb	0.37±0.06	5.59±0.90	<0.00003*	<0.01*	15.1
Sb	0.0344±0.0069	0.0032±0.0005	0.00011*	<0.01*	0.09
Se	<0.1	0.43±0.04	<0.00001*	<0.01*	>4.30
Sn	0.113±0.023	0.042±0.006	0.0067*	<0.01*	0.37
Sr	0.52±0.07	1.19±0.14	0.00031*	<0.01*	2.29
Th	0.0050	0.0017	-	-	>0.34
Ti**	0.76±0.13	2.45±0.55	0.0091*	<0.01*	3.22
Tl	<0.0001	0.0014±0.0002	<0.00001*	<0.01*	>14.0
U	<0.0001	0.0024±0.0008	0.012*	<0.01*	>24.0
V	0.012	0.188±0.036	0.00021*	<0.01*	>15.7
W	0.080±0.030	0.033±0.008	0.152	>0.05	0.41
Zn	5.1±0.7	35.4±4.4	<0.00001*	<0.01*	6.94
Zr	<0.010	0.016±0.003	0.048*	<0.05*	>1.6

*M – arithmetic mean, SEM – standard error of mean, t-test - Student's t-test, U-test - Wilcoxon-Mann-Whitney U-test, * Significant values.*

Table 3. Median, minimum and maximum value of means of trace element mass fractions (mg/kg dry tissue) in normal breast tissue of females according to data from the literature in comparison with this work results.

Element	This work results		Published data [Reference]	
	M±SD n=38	Median of means (n)*	Minimum of means M or M±SD, (n)**	Maximum of means M or M±SD, (n)**
Al	3.42±1.98	3.5 (4)	0.103 (52) [40]	38.4 (20) [41]
As	0.030±0.015	0.48 (3)	0.095 (3) [42]	<5 (-) [43]
B	0.170±0.084	<0.16 (1)	<0.16 (-) [43]	<0.16 (-) [43]
Ba	0.174±0.148	3.1 (2)	0.030(-) [43]	6.24±0.59 (-) [44]
Bi	0.014±0.018	<0.06 (1)	<0.06 (-) [43]	<0.06 (-) [43]
Cd	0.047±0.033	0.034 (5)	0.0310 (8) [45]	<0.4 (-) [43]
Ce	0.0066±0.0038	0.0012 (1)	0.0012 (1) [46]	0.0012 (1) [46]
Co	0.0067	<0.04 (3)	0.0360±0.0008 (18) 47]	0.06 (20) [41]
Cr	0.288±0.157	0.088 (7)	0.0012(1) [46]	2.44±0.23 (-) [44]
Cs	0.0036	0.0008 (1)	0.0008(1) [46]	0.0008(1) [46]
Cu	0.872±0.555	2.56 (19)	0.4(1) [46]	2280±140 (-) [48]
Ga	0.0053	0.005 (2)	0.004(1) [46]	<0.006 (-) [43]
Ge	0.0055	0.0004 (1)	0.0004(1) [46]	0.0004(1) [46]
La	0.0062±0.0047	<0.6 (1)	<0.6 (-) [43]	<0.6 (-) [43]
Li	0.0117±0.0047	-	-	-
Mg	20.8±13.0	85.5 (4)	4.5±0.9 (-) [44]	680 (4) [49]
Mn	0.128±0.138	0.5 (7)	0.06 (-) [43]	3.74 (4) [49]
Mo	0.0091	0.22 (4)	0.008(1) [46]	0.22 (20) [41]
Nb	0.012±0.014	<0.3 (2)	0.0004(1) [46]	<0.6 (-) [43]
Nd	0.0013	-	-	-
Ni	0.299±0.315	0.16 (7)	0.01(1) [46]	1.14 (20) [41]
Pb	2.16±2.72	0.128 (6)	0.0081(1) [46]	3.21±2.15 (16) [44]
Rb	0.368±0.360	626 (2)	0.2(1) [46]	2504 (4) [49]
Sb	0.0344±0.0357	0.044 (2)	0.030-0.044 (2) [42]	5.0 (-) [43]
Se	<0.1	0.22 (5)	0.062±0.016 (6) [50]	1.42 (8) [51]
Sn	0.113±0.114	0.52 (1)	0.52 (-) [43]	0.52 (-) [43]
Sr	0.522±0.376	0.2 (4)	0.12 (-) [43]	0.70±0.22 (16) [44]
Th	0.00503	-	-	-
Ti	0.76±0.50	0.13 (2)	<0.1 (-) [43]	0.16(1) [46]
Tl	<0.0001	0.006 (3)	0.0006 (1) [52]	<0.08 (-) [43]
U	<0.0001	<0.002 (3)	0.0004 (1) [46]	0.0060±0.0006 (3) [53]
V	0.012	<0.008 (1)	<0.008 (-) [43]	<0.008 (-) [43]
W	0.080±0.104	-	-	-
Zn	5.08±3.71	8.3 (17)	2.88 (46) [54]	27.8±5.0 (20) [55]
Zr	<0.01	<0.42 (2)	0.032 (8) [56]	<0.8 (-) [43]

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

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

Element	**This work results**		**Published data [Reference]**	
	M±SD n=17	**Median of means (n)***	**Minimum of means M or M±SD, (n)****	**Maximum of means M or M±SD, (n)****
Al	11.9±7.4	50.5 (1)	50.5±23.9 (61) [57]	50.5±23.9 (61) [57]
As	0.061±0.027	-	-	-
B	0.73±0.46	-	-	-
Ba	0.17±0.11	-	-	-
Bi	0.0105±0.0079	-	-	-
Cd	0.182±0.198	0.58 (3)	0.185 (50) [58]	231±456 (14) [59]
Ce	0.0092±0.0054	-	-	-
Co	0.0078±0.0043	0.090 (3)	0,027±0,025 (23) [60]	6,75±9,85 (61) [57]
Cr	0.38±0.20	0.845 (3)	0.80±0.11d (68) [61]	1.85±2.90 (61) [57]
Cs	0.012±0.007	0.010 (1)	0.0088±0.0072 (-) [60]	0.017±0.012 (-) [60]
Cu	3.04±1.07	6.00 (9)	1.80±0.41 (18) [47]	99±114 (14) [59]
Ga	0.0052	-	-	-
Ge	0.0057	0.69 (1)	0.69±0.39 (68) [62]	0.69±0.39 (68) [62]
La	0.0079±0.0079	-	-	-
Li	0.017±0.012	3.4 (1)	3.4±3.2 (61) [57]	3.4±3.2 (61) [57]
Mg	265±159	168 (2)	19.6±5.4 (11) [63]	317±438 (61) [57]
Mn	0.33±0.20	1.07 (3)	0.90±1.05 (61) [57]	1.25±0.50 (50) [55]
Mo	0.031±0.022	7.85 (1)	7.85±7.70 (61) [57]	7.85±7.70 (61) [57]
Nb	0.0051±0.0053	-	-	-
Nd	0.0042±0.0061	-	-	-
Ni	0.136±0.106	0.49 (3)	0.47±0.10 (68) [61]	10.4±15.1 (61) [57]
Pb	0.165±0.136	2.42 (4)	1.13±0.13 (68) [61]	37.1±119.5 (61) [57]
Rb	5.59±3.72	2.2 (3)	0.50±0.09 (68) [61]	8.8±5.8 (-) [60]
Sb	0.0032±0.0021	0.35 (2)	0.064±0.049 (-) [60]	21.3±11.2d (61) [57]
Se	0.43±0.16	0.515 (7)	0.315±0.090 (22) [64]	1.62 (7) [65]
Sn	0.042±0.026	-	-	-
Sr	1.19±0.59	20.6 (1)	20.6±28.2 (61) [57]	20.6±28.2 (61) [57]
Th	0.0017	-	-	-
Ti	2.45±2.13	-	-	-
Tl	0.0014±0.0008	-	-	-
U	0.0024±0.0034	-	-	-
V	0.188±0.145	-	-	-
W	0.033±0.030	-	-	-
Zn	35.4±18.0	35.6 (10)	15±8 (-) [60]	253±179 (14) [59]
Zr	0.016±0.012	-	-	-

M - arithmetic mean, SD – standard deviation

Table 5. Ratio of median of mean mass fractions of trace element (mg/kg dry tissue) in the benignly transformed (BT) and normal (N) breast tissue according to literature data in comparison with this work results.

Element	Medians of the reported means (n)*			This work result
	BT tissue	N tissue	Ratio BT to N	Ratio BT to N
Al	50.5 (1)	3.5 (4)	14.4	3.48
As	-	0.48 (3)	-	2.03
B	-	<0.16 (1)	-	4.29
Ba	-	3.1 (2)	-	0.98
Bi	-	<0.06 (1)	-	0.75
Cd	0.58 (3)	0.034 (5)	17.1	3.87
Ce	-	0.0012 (1)	-	1.39
Co	0.090 (3)	<0.04 (3)	>22.5	>1.16
Cr	0.845 (3)	0.088 (7)	9.60	1.32
Cs	0.010 (1)	0.0008 (1)	12.5	>3.51
Cu	6.00 (9)	2.56 (19)	2.34	3.49
Ga	-	0.005 (2)	-	>0.98
Ge	0.69 (1)	0.0004 (1)	1725	>1.04
La	-	<0.6 (1)	-	1.27
Li	3.4 (1)	-	-	1.45
Mg	168 (2)	85.5 (4)	1.96	12.7
Mn	1.07 (3)	0.5 (7)	2.14	2.58
Mo	7.85 (1)	0.22 (4)	35.7	>4.44
Nb	-	<0.3 (2)	-	0.42
Nd	-	-	-	3.23
Ni	0.49 (3)	0.16 (7)	3.06	0.45
Pb	2.42 (4)	0.128 (6)	18.9	0.08
Rb	2.2 (3)	626 (2)	0.0035	15.1
Sb	0.35 (2)	0.044 (2)	7.95	0.09
Se	0.515 (7)	0.22 (5)	2.34	>4.30
Sn	-	0.52 (1)	-	0.37
Sr	20.6 (1)	0.2 (4)	103	2.29
Th	-	-	-	>0.34
Ti	-	0.13 (2)	-	3.22
Tl	-	0.006 (3)	-	>14.0
U	-	<0.002 (3)	-	>24.0
V	-	<0.008 (1)	-	>15.7
W	-	-	-	0.41
Zn	35.6 (10)	8.3 (17)	4.29	6.94
Zr	-	<0.42 (2)	-	>1.6

(n) – the number of all found articles for each chemical element.*

± standard deviation or median) of the mass fraction of each TE found from the reported data; the number of samples studied is indicated in parentheses and the corresponding link is given in square brackets.

A comparison of the ratio of the mean mass fraction of TEs in the benignly transformed and normal beast tissue obtained in this work with the corresponding ratios calculated from published results are presented in Table 5. To obtain the corresponding ratios according to the literature, we used the median values of the mass fractions of TEs in the benignly transformed and normal beast tissue.

Discussion

Acceptable agreement of the values of the content of TEs in the international certified reference materials MODAS-5 (Cod tissue), MODAS-3 (Herring tissue), IAEA-153 (Milk powder) obtained in this study with the data of the corresponding certificates (Table 1) indicates sufficient accuracy of the developed ICP-MS micro method and reliability of 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 samples of benignly transformed and normal breast tissue, presented in Fig.1 and Tables 2-5.

Mass fractions of the overwhelming majority of TEs were determined in all or most samples of both benign transformed and normal breast tissue. This allowed us to calculate the main statistical characteristics for the mass fractions of these TEs, such as the arithmetic mean (M), standard deviation of the mean (SD) and standard error of the mean (SEM) (Tables 2-5). In all normal breast tissue samples the contents of Se, Tl, U and Zr were below the detection limits of our ICP-MS method, while the levels of Co, Cs, Ga, Ge, Mo, Nd, Th and V were detected only in a few samples. In all benignly transformed breast tissue samples, only Ga, Ge, and Th content were determined in several samples. This allowed us to calculate the possible upper limit of the mean value (Mmax) for these TEs using equation 1.

The M, SD and SEM values are valid only if the results of determination of the content of TEs in the studied samples are distributed normally. Only after ensuring that the distribution of results within each of the two groups of samples being studied (benignly transformed and normal breast tissue) is normal, can M, SD and SEM be used for comparison using parametric tests such as Student's t-test. However, reliable detection of normal distribution of results with a relatively small number of samples in the presented study (n=17 and n=38, respectively) is impossible, since the existing criteria for detection of the type of distribution of results require a large sample size, usually several hundred samples. Since in our study it was not possible to prove or disprove the "normality" of the distribution of the obtained results due to the small sample size, in addition to the parametric Student's t-test, the nonparametric Wilcoxon-Mann-Whitney U-test was also used, which is applicable to any type of distribution of the results of the content of TEs in breast tissue.

To assess the effect of benign transformation of breast tissue on the content of TEs in it, a comparison of the elemental composition of benignly transformed and normal breast tissue was performed (Table 2). In benignly altered tissue, the mass fractions of all studied elements, with the exception of Ba, Bi, Ga, Nb, Ni, Pb, Sb, Sn, Th, and W exceeded the levels characteristic of normal breast tissue. To compare the two groups of samples (benignly transformed and normal breast tissue), both the parametric Student's t-test and the nonparametric Wilcoxon-Mann-Whitney U-test were used, and both criteria confirmed the reliability of the difference in the mass fractions of such TEs as Al, As, B, Cd, Cs, Cu, Mg, Mn, Mo, Ni, Pb, Rb, Sb, Se, Sn, Sr, Ti, Tl, U, V, Zn, and Zr.

In the study of TEs in the mammary gland in norm and pathology, both tissue samples obtained from healthy women and samples of visually intact tissue adjacent to the benign or malignant lesion are used as the "norm". However, mixing these two groups of samples is incorrect. For example, we have previously shown that in terms of the TEs content, intact tissue adjacent to thyroid tumors is not identical to normal thyroid tissue in practically healthy individuals [71,72]. Therefore, in our review of the literature (Table 3), only the results obtained from studies of breast tissue samples from healthy women were used. Some values of the mass fractions of TEs were not expressed by the authors of the cited works in terms of dry tissue. However, we calculated these values using literature data on the water content of 50% [73] and ash content of 1% (in dry tissue) [74] in the mammary gland of adult women.

When considering the published data in tables 3 and 4, attention is drawn to the huge difference between the minimum (column 4) and maximum (column 5) values, which for almost all TEs is one, two, and even three 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 analysis result. Since 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 breast tissue should approach the true value. This interpretation of the existing spread of accumulated data allows us to compare our results (column 2) with the medians of published mean mass fractions (column 3) for each TE.

As follows from the data in Table 3, the median values of the literature data on TEs 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 and fit within their range (min - max). Our measurements of the mass fractions of Ba, Mo, Nb, Pb, Rb, and Se were within the range of published mean values for TEs content in normal breast tissue, but our data for As, Co, Tl, U, and Zr content 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 (Table 3).

The values of the mean mass fractions of TEs in benignly transformed breast tissue that we obtained were in good agreement with the median values of published data (Table 4). The only exceptions were Co, Ge, Li, Mo, Pb, Sb, and Sr. The results we obtained for Co and Pb were one order of magnitude lower, and for Sb two orders of magnitude lower, than the corresponding median values found from published data. For Ge, Li, Mo, Pb, Sb, and Sr content we found only one paper in the literature. In the available literature, no data on the content of As, B, Ba, Bi, Ce, Ga, La, Nb, Nd, Sn, Th, Ti, Tl, U, V, W, and Zr in benignly transformed breast tissue were found.

If to use the ratios of median values of mean mass fractions of TEs in normal and benignly transformed breast tissue, found from the analysis of literature data (Tables 3 and 4, respectively), they can be compared with the corresponding ratios of mean values of TEs content in these tissues obtained in the present study and presented in Table 2. Calculation of these ratios showed that the increase in the content of almost all studied TEs during benign transformation of breast tissue discovered in the present study agreed with the results we obtained from the analysis of published data (Table 5). The only exceptions were the results for Ni, Pb, Rb, and Sb. Thus, both from the data obtained in the present study and from our calculations made based on literature data, it clearly followed that the content of such elements as Al, Cd, Co, Cr, Cs, Cu, Mg, Mn, Mo, Se, Sr, and Zn in benignly transformed tissue is higher than in normal breast tissue (Table 5).

For a few TEs (Al, Cd, Cu, Mg, Mo, Se, and Zn) this increase was multiple (3 or more times). Such significant changes suggest the potential possibility of using the level of these TEs in the lesion of the mammary gland as bioindicators of BBD. The use of TEs levels in transformed breast tissue as BBD markers seems to be very promising, since the capabilities of modern nuclear analytical methods are rapidly increasing. For example, the distribution of such diagnostically promising TE as Zn in the mammary gland can be determined non-invasively using neutron stimulated emission computed tomography [75].

One of the possible explanations for the observed phenomenon of multiple increase in the content of TEs in benignly transformed tissue may be associated with structural changes in the tissue, since the content of TEs in various morphological structures is different, as well as with disturbances in the intracellular metabolism of TEs that occur when the mechanisms regulating the proliferation of cells break down. As a result of such disturbances, a change in the permeability of cell membranes and subsequent excessive accumulation of TEs in cells may occur.

Another possible explanation may be associated with excessive intake of TEs into the body with food, water and air due to uncontrolled changes in the content of TEs in the environment. Even a slight increase in the intracellular concentration of such metals as Cu and Zn, the levels of which are under conditions of strict homeostasis, can provoke the process of excessive proliferation of cells. A similar effect can also be caused by increased levels of potentially tumorigenic metals, such as Cd. In this case, an increase in the content of these TEs should be detected not only in transformed tissue, but also in visually intact tissue adjacent to the lesion of the mammary gland. To confirm or refute the possibility of such a variant of the development of BBD, we plan to compare the content of TEs typical of breast tissue in healthy women with the levels of TEs in samples of visually intact tissue adjacent to the benign lesions.

As for the limitations of the present study, first, it should be noted that the sample size of the studied samples of benignly transformed (n=17) and normal breast tissue (n=38) was relatively small. This did not allow us to determine the content of TEs considering the histological structure of the transformed tissue, which is of particular interest for diagnostics, prognosis and choice of treatment tactics. Therefore, we plan to continue collecting samples and analyzing the material obtained.

The revealed multiple increase in the content of TEs in benignly transformed breast tissue opens up great prospects for the development of new in vitro and in vivo methods for differential diagnostics of BBD and BC, in which TEs levels will act as tumor markers. For this purpose, further study of the content of TEs in the tissue of the lesion in benign and malignant diseases of the mammary gland and comparison of the obtained results are necessary. We plan to conduct such studies in the future. The revealed multiple increase in the content of TEs in benignly transformed breast tissue opens up great prospects for the development of new in vitro and in vivo methods for differential diagnostics of BBD and BC, in which TEs levels will act as tumor markers. For this purpose, further study of the content of TEs in the tissue of the lesion in benign and malignant diseases of the mammary gland and comparison of the obtained results are necessary. We plan to conduct such studies in the future.

Conclusion

The developed method of sample preparation allows us to obtain reliable data of 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 samples of benignly transformed and normal breast tissue with the help of ICP-MS. An important feature of the developed method is the ability to determine the content of TEs in samples weighing only a few milligrams, which allows it to be used for analyzing puncture biopsy materials. In the present study, a significant increase in the content of all the studied TEs in the breast tissue during its benign transformation, except for Ba, Bi, Ga, Nb, Ni, Pb, Sb, Sn, Th, and W, was revealed. All the differences revealed were generally agreed with the results of our analytical review of the literature. The results obtained in this work provide a solid basis for the development of new methods for diagnosing BBD based on the use of the level of TEs in the tissue of the breast lesion. Further detailed studies are needed to clarify the role of accumulation of many TEs in benignly transformed tissue in the etiology and pathogenesis of BBD. Our further studies will be aimed at increasing the sample size, as well as studying the content of TEs in malignant breast tumors.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

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Authors' contributions

Conception and design of the study, statistical analysis, data analysis and interpretation, manuscript preparation and review: Zaichick V. Experimental studies, data acquisition, diagram design: Dogadkin D, Experimental studies, data acquisition: Gromyak I Experimental studies, data acquisition: Shirokova V. Manuscript editing, data interpretation, administrative support: Kolotov V.

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