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(Research Article)

Association between trace element contents in normal human breast and age investigated using inductively coupled plasma mass spectrometry

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Abstract

The etiology of breast cancer remains largely unclear; however, it is well known that the incidence of this disease increases with age. In the presented work, for the first time, the age-related changes of Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mg, Mn, Nb, Ni, Pb, Rb, Sb, Sn, Sr, Ti, W, and Zn content in the mammary gland of women aged 16-60 years was investigated. For this purpose, a method based on inductively coupled plasma mass spectrometry (ICP-MS) was employed, which makes it possible to determine the mass fractions of these trace elements in microsamples (mass from 10 mg) of breast tissue. With the help of this method, the material obtained during the autopsy of 38 practically healthy women aged 16-60 years who died suddenly was studied. Trace element mass fractions were determined in two age groups of women: 16-40 and 41-60 years old. Using the parametric Student's t-test and the non-parametric Wilcoxon-Mann-Whitney U-test to compare two age groups, as well as Pearson's correlation coefficients between age and trace elements mass fractions, it was found that the Cu, Mg, Rb, and Zn mass fractions in normal breast tissue decrease with age, while the As mass fraction increase. The phenomenon of the age-related changes of trace elements mass fractions in the normal mammary gland, discovered for the first time, requires further detailed study.

Keywords: Woman mammary gland; Age-related changes; Trace elements; Inductively coupled plasma mass spectrometry

1. Introduction

Breast cancer (BC) is the most common global malignancy and the leading cause of cancer deaths among women aged 35–54 [1,2]. The high morbidity and mortality from BC among able-bodied women make the problem of diagnosing and treating this disease not only an urgent medical, but also a social task [3]. The relevance of the problem of BC is due, first of all, to the steady increase in the frequency of this pathology around the world. Despite numerous studies, the etiology of BC remains largely unclear, although many candidates have been found that increase the risk of this disease and, first of all, such as individual genetic characteristics, age, and adverse environmental factors [4]. Since the change in the human gene pool is rather slow, it can be assumed that the alarmingly rapid increase in the incidence of breast cancer is associated primarily with the rate of age-related changes in the body and the transformations taking place in the environment. The age-related incidence of breast cancer in women in Europe and North America shows a continuous growth with a maximum at the age of 40-60 years [5].

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The steady development of industry, chemistry and technology in agriculture, food production, pharmaceuticals, medicine, cosmetics, especially over the past 100 years, has led to global changes in the quality of the human environment [6]. These changes also concern the amount of trace elements (TE) entering the human body. The ability of the mammary gland during lactation to accumulate significant amounts of TE for milk production [7] indicates a special elemental composition of the gland tissue.

Our previous studies have shown that TE homeostasis plays an important role in the normal and pathophysiology of human bones, thyroid, and prostate glands. Moreover, it has been found that mass fractions of many TE in bones, thyroid and prostate glands depend on age [6,8-39]. From this it can be assumed that the specific physiological factors of the human mammary gland probably play a key role not only in the normal physiology of the mammary gland, but also in the etiology of various diseases of this organ, including BC. Despite the understanding of the important role of TE, surprisingly little is known about the involvement of TE in the normal and pathological physiology of the human breast.

There are few studies about TE in the mammary gland of women [40-50]. However, the published data completely lacks information on age-related changes in TE mass fractions in breast tissue.

The main objective of this study was to determine the Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mg, Mn, Nb, Ni, Pb, Rb, Sb, Sn, Sr, Ti, W, and Zn mass fractions in the mammary gland of healthy women comprising two age groups (16-40 years and 41-60 years) using inductively coupled plasma mass spectrometry(ICP-MS). The second goal was to evaluate the results obtained. The third goal was to compare the mean mass fractions of Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mg, Mn, Nb, Ni, Pb, Rb, Sb, Sn, Sr, Ti, W, and Zn in normal breast tissue obtained during the study with reported data. The final aim was to find differences and correlations between mean TE mass fractions values obtained for normal breast tissue and age.

2. Material and Methods

2.1. Samples

Frozen breast tissue samples supplied by the Forensic Medical Examination Department of the City Hospital, Obninsk, Russia were analyzed. A randomized sample of normal breast tissue was obtained from autopsies of 38 women (age 16 to 60 years, Caucasian race, Caucasian lifestyle) during the first day after sudden death. Typical causes of death for most women were car accidents and injuries. All of the dead women were residents of Obninsk, a small town (about 120,000 inhabitants) in a non-industrial area 105 kilometers southwest of Moscow. Written informed consent was obtained from relatives of the victims during sampling. The study was performed according to the standards of the Institutional Ethics Committee and the Helsinki declaration of 1975, as revised in 1983, and was approved by the Ethical Committees of the Medical Radiological Research Centre, Obninsk.

Tissue samples from all victims weighing about 10 g were taken in the right mammary gland in its lower inner quadrant. A scalpel made of high-purity titanium was used for sampling [51]. Available clinical data were reviewed for each subject. None of the individuals had a history of an intersex condition, endocrine disorder, neoplasm, or other chronic disease that would interfere with normal breast development. None of the individuals received drugs that affect the morphology of the mammary gland and TE mass fraction in the gland. The collection of samples was divided into two age groups of females: 16-40 and 41-60 years old.

2.2. Sample preparation

One of the goals to determine TE mass fractions in the mammary gland in normal and pathological conditions was the search for markers of BC and the development of new diagnostic methods by determining the TE mass fractions in puncture biopsies of the lesion. When examining a patient with a single puncture biopsy, a material weighing about 10-20 mg can be obtained. Therefore, we employed a sample decomposition method in acid digestion assisted by microwave radiation. Breast tissue samples of small mass (from 10 mg) were digested for subsequent determination of TE in them using ICP-MS [52]. To this end, a MARS-5 microwave oven system (from CEM Corporation) equipped with Teflon flasks (capacity for 100 cm^3) accompanied with mini vessels was used. About 10 mg or more mass of samples was placed in each mini vessel. In each mini-vessel 1.4 ml of high-purity nitric acid (HNO_3) was added. The mini-vessels were closed with their respective stoppers, the stoppers were fixed with a lid and then the mini-vessels were placed in the Teflon flask. Three assemblies of these mini-vessels were enclosed in the Teflon flask. Analytical grade HNO_3 (12.5 ml) was added to the Teflon flask to provide a vapor pressure equal to the pressure of acids in mini vessels. The Teflon flasks with mini-vessels were placed in the rotor that was then placed in the microwave oven system. One of the flask contained temperature and pressure sensors. The samples were heated to 150°C for 15 min and hold for 20 min at this temperature. The radiation power was 800 W at a frequency of 2450 MHz. After cooling to 30^{0}C the contents of the mini-vessels were quantitatively transferred into 10 ml tubes and the solutions were adjusted to 10 ml with 2% (v/v) HNO_3 solution. For measurements of Zn, As and Se, the sample solutions obtained were diluted five times with distilled water. For measurements of the rest of elements, the solutions were diluted twice with distilled water.

2.3. Reagents, calibration, and certified reference materials

Deionized water distilled without boiling in a PTFE Subboiler ECO IR Maassen (from Germany) and HNO_3 (65% m/m) from Merck (Germany) were used to prepare solutions and samples. This acid was purified by sub boiling distillation using the PTFE Subboiler ECO IR Maassen system. The calibration solutions prepared by serial dilution of reference solutions supplied by High-Purity Standards (High-Purity Standards, North Charleston, SC, USA), Element Standards ICP-MS-68A (Solution A and Solution B, 68 elements) and single-element solutions of B, Mg, Al, Mn, Ni, Cu, Zn, Se, Rb, Sr, Cs, Ba.

Solutions containing 10, 25 and 50 µg/L of specific elements were prepared from solution A (10 mg/L), solutions containing 5 and 10 µg/L were prepared from solution B (10 mg/L). Single-element solutions (10 mg/L) were diluted to 500 µg/L for B, Mg, Al, Mn, Ni, Cu, Zn, Sr, Ba and to 20, 75 and 100 µg/L for Se, Rb, Cs. In all cases, 2%(v/v) HNO_3 was used as a diluent. The solutions were diluted before measurement in disposable polypropylene test tubes of the volume 10 or 50 mL (Litaplast-Med, Belarus). The gravimetric method was used to determine the degree of dilution. To control the signal drift during the measurements using ICP-MS indium (In) was used as an internal standard, which was added to the calibration and sample solutions, at a concentration of 10 µg/L. Trace Elements in Drinking Water Standard CRM-TMDW (26 elements) were analyzed to check the ICP-MS performance. The CRM-TMDW was used as received.

To check the reliability of the results obtained, three certified reference materials (CRMs) were analyzed; the Polish certified reference materials MODAS-5 (Cod Tissue) and MODAS-3 (Herring Tissue), as well as the reference material prepared by the International Atomic Energy Agency IAEA-153 (Powdered milk) were used.

~~*2.4.*~~ ICP-MS measurements

An X Series II inductively coupled plasma quadrupole mass spectrometer (Thermo Scientific, Germany) equipped with a concentric nebulizer and a quartz cyclonic spray chamber cooled by a Peltier element (2°C) was employed. The parameters were as follows. Plasma power: 1400 W, plasma gas (argon) flow rate: 13 L/min, auxiliary gas (argon) flow rate: 1.25 L/min, nebulizer gas (argon) flow rate: 0.88 L/min, plasma sampling depth: 105 rel. units and sample flow rate: 1 mL/min. Mass spectra were acquired using two scanning modes: (1) panoramic (Survey Scan) with 5 passes from 5 to 244 m/z and (2) at points (Peak Jumping) with 1 channel per weight, the integration time of 20 ms, and with 25 passes. All measurements were performed using PlasmaScreen software. 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 (Ba^{2+}/Ba^+) is no more than 3%.

2.5. Data collection and processing

The ICP–MS data were processed using the iPlasmaProQuad software developed in the laboratory of Vernadsky Institute [58]. This program was designed to process information output from the X Series II quadrupole mass spectrometer. The program involves data from calibration,-element concentrations calculation, and corrections (the mass spectrometer is used only as an isotope mass detector). This approach gives complete control over the processing and estimation of the uncertainty of the measurement results, which is important both for the subsequent use of the results of analysis in other fields and for monitoring the analysis performance.

2.6. Statistics

The main statistical parameters, such as the arithmetic mean, standard deviation, standard error of the mean, minimum and maximum values, median, percentiles with levels of 0.025 and 0.975 for mass fractions of TE (mg kg^{-1} of dry mass) were calculated using the Microsoft Office Excel program. The reliability of difference in the results between two age groups was evaluated by the parametric Student's t-test and nonparametric Wilcoxon-Mann-Whitney U-test. For the estimation of the Pearson correlation coefficient between age and TE mass fraction the Microsoft Office Excel program was also used.

3. Results

Table 1 depicts the mass fractions of TE determined in the CRM MODAS-5 (Cod Tissue), MODAS-3 (Herring Tissue) and IAEA-153 (Powdered milk).

Arithmetic mean of Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mg, Mn, Nb, Ni, Pb, Rb, Sb, Sn, Sr, Ti, W and Zn. mass fractions in normal breast tissue of healthy women aged 16-40 years and 41-60 years are presented in tables 2 and 3, respectively. In addition to the arithmetic mean, some other statistical indicators were included in these tables, such as standard deviation, standard error of the mean, minimum and maximum values, median, percentiles with levels of 0.025 and 0.975. Comparison of the results of the present work with data reported for the mass fractions of Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mg, Mn, Nb, Ni, Pb, Rb, Sb, Sn, Sr, Ti, W, and Zn in normal breast tissue of adult women is shown in Table 4.

Differences between the mean values of mass fractions of Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mg, Mn, Nb, Ni, Pb, Rb, Sb, Sn, Sr, Ti, W, and Zn in normal breast tissue of healthy women aged 16-40 and 41-60 years evaluated by the parametric Student's *t*-test and nonparametric Wilcoxon-Mann-Whitney *U*-test are presented in Table 5.

Table 1 Results (Mean±SD) for 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**	
	Certified	Found	Certified	Found	Certified	Found
Ag	-	-	0.04±0.01	0.039±0.003	-	-
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	1180±40	3000±200	2740±80	1060±75	1020±20
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
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	-	-	-	-
Y	-	-	0.0096	0.009±0.003	-	-
Zn	20.1±1.1	21±1	111±6	114±3	39.5±1.8	33±1

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

Table 2 Basic statistical parameters of 23 trace elements mass fraction (mg kg^{-1}, dry tissue) in the normal breast tissue of females 16–40 years old.

Element	Mean	SD	SEM	Min	Max	Med.	P0.025	P0.975
Al	4.01	2.27	0.66	1.26	7.36	3.80	1.26	7.28
As	0.018	0.014	0.004	0.0010	0.0430	0.018	0.0010	0.0423
B	0.186	0.100	0.033	0.068	0.380	0.164	0.0730	0.364
Ba	0.202	0.171	0.046	0.0270	0.601	0.160	0.0296	0.580
Bi	0.015	0.021	0.007	0.0010	0.0620	0.0072	0.00115	0.0562
Cd	0.043	0.033	0.008	0.0102	0.126	0.0340	0.0114	0.123
Ce	0.0074	0.0045	0.0012	0.0018	0.0160	0.0075	0.00193	0.0154
Cr	0.294	0.173	0.039	0.0697	0.661	0.291	0.0836	0.643
Cu	1.07	0.61	0.14	0.295	2.63	0.949	0.321	2.40
La	0.0070	0.0058	0.0016	0.00180	0.0240	0.0044	0.00210	0.0199
Li	0.0132	0.0043	0.0019	0.00690	0.0190	0.0133	0.00744	0.0185
Mg	21.3	8.0	2.1	10.0	35.0	19.0	10.7	34.7
Mn	0.151	0.171	0.039	0.0460	0.774	0.095	0.0460	0.611
Nb	0.0085	0.0031	0.0014	0.0050	0.0122	0.0099	0.00505	0.0120
Ni	0.138	0.076	0.017	0.0330	0.303	0.116	0.0340	0.288
Pb	1.74	1.65	0.38	0.200	5.74	1.19	0.227	5.43
Rb	0.502	0.421	0.097	0.111	1.71	0.359	0.126	1.53
Sb	0.0265	0.0247	0.0064	0.0100	0.101	0.0170	0.0100	0.0846

Sn	0.106	0.071	0.019	0.0360	0.251	0.0775	0.0386	0.243
Sr	0.579	0.463	0.103	0.0550	1.91	0.473	0.0783	1.67
Ti	1.01	0.62	0.23	0.190	1.93	0.830	0.261	1.90
W	0.100	0.132	0.054	0.00200	0.335	0.031	0.00438	0.316
Zn	4.64	3.51	0.78	1.58	14.9	3.55	1.58	13.5

M – arithmetic mean, 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.

Table 3 Basic statistical parameters of 23 trace elements mass fraction (mg kg^{-1}, dry tissue) in the normal breast tissue of females 41–60 years old.

Element	**Mean**	**SD**	**SEM**	**Min**	**Max**	**Med.**	**P0.025**	**P0.975**
Al	2.78	1.45	0.44	1.21	5.54	2.13	1.28	5.42
As	0.036	0.017	0.005	0.0100	0.0640	0.038	0.0116	0.0615
B	0.149	0.057	0.021	0.069	0.212	0.169	0.0737	0.211
Ba	0.129	0.096	0.032	0.0370	0.356	0.100	0.0398	0.321
Bi	0.013	0.015	0.006	0.0020	0.0429	0.0081	0.00218	0.0393
Cd	0.054	0.033	0.010	0.0140	0.114	0.049	0.0157	0.112
Ce	0.0055	0.0023	0.0007	0.0029	0.0090	0.0054	0.00293	0.00885
Cr	0.278	0.138	0.037	0.0420	0.496	0.256	0.0644	0.478
Cu	0.558	0.192	0.053	0.295	0.905	0.517	0.303	0.869
La	0.0052	0.0027	0.0008	0.0016	0.0094	0.0051	0.00168	0.00931
Li	0.0103	0.0050	0.0022	0.0057	0.0186	0.0088	0.00587	0.0178
Mg	15.3	5.5	1.5	10.0	26.0	13.0	10.3	25.7
Mn	0.091	0.042	0.012	0.042	0.200	0.086	0.0423	0.178
Nb	0.013	0.017	0.006	0.0033	0.0551	0.0069	0.00332	0.0485
Ni	0.154	0.105	0.029	0.027	0.319	0.109	0.0308	0.316
Pb	2.89	3.94	1.19	0.443	13.0	0.94	0.474	11.7
Rb	0.187	0.105	0.028	0.0920	0.467	0.163	0.0936	0.424
Sb	0.044	0.045	0.013	0.0090	0.145	0.021	0.00983	0.139
Sn	0.122	0.160	0.051	0.035	0.564	0.061	0.0355	0.474
Sr	0.442	0.185	0.049	0.130	0.718	0.425	0.130	0.697
Ti	0.64	0.53	0.20	0.240	1.77	0.45	0.257	1.63
W	0.060	0.073	0.030	0.0087	0.201	0.036	0.00911	0.184
Zn	3.02	0.89	0.25	1.90	4.60	2.65	1.96	4.43

M – arithmetic mean, 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

Table 4 Median, minimum and maximum value of means of chemical element mass fractions (mg kg^{-1}, dry mass basis) in normal breast tissue of adult females according to reported data in comparison with this work results

	Published data [Reference]			**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=38
Al	6.7 (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
Cr	0.088 (7)	0.0012(1) [46]	2.44±0.23 (-)[44]	0.29±0.16
Cu	2.56 (19)	0.4(1) [46]	2280±140 (-) [47]	0.87±0.54
La	<0.6 (1)	<0.6 (-) [43]	<0.6 (-) [43]	0.0062±0.0047
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) [48]	0.13±0.14
Nb	<0.3 (2)	0.0004(1) [46]	<0.6 (-) [43]	0.012±0.014
Ni	0.16 (7)	0.01(1) [46]	1.14 (20)[41]	0.144±0.087
Pb	0.128 (6)	0.0081(1) [46]	3.21±2.15 (16) [44]	2.2±2.7
Rb	626 (2)	0.2(1) [46]	2504 (4) [48]	0.37±0.36
Sb	0.044 (2)	0.030-0.044 (2) [42]	5.0 (-) [43]	0.034±0.036
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±0.38
Ti	0.13 (2)	<0.1 (-) [43]	0.16(1) [46]	0.83±0.59
W	-	-	-	0.08~~0~~±0.104
Zn	8.3 (17)	2.88 (46) [49]	27,8±5,0 (20) [50]	4.00±2.87

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

Table 5 Comparison of mean values (M±SEM) of Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mn, Nb, Ni, Pb, Rb, Sb, Sn, Sr, Ti, W, and Zn mass fraction (mg/kg, dry mass basis) in normal female breast tissue of two age groups (AG)

Element	**Female "normal" breast tissue**				**Ratio**
	AG1 16-40 years n=22	AG2 41-60 years n=16	t-test *p*£	U-test p	AG2 to AG1
Al	4.01±0.66	2.78±0.44	0.13	>0.05	0.69
As	0.018±0.004	0.036±0.005	0.013*	<0.01*	2.00
B	0.186±0.033	0.149±0.021	0.356	>0.05	0.80
Ba	0.202±0.046	0.129±0.032	0.205	>0.05	0.64
Bi	0.015±0.007	0.013±0.006	0.846	>0.05	0.87

Cd	0.043±0.008	0.054±0.010	0.394	>0.05	1.26
Ce	0.0074±0.0012	0.0055±0.0007	0.206	>0.05	0.74
Cr	0.294±0.039	0.278±0.037	0.756	>0.05	0.95
Cu	1.07±0.14	0.558±0.053	0.002*	<0.01*	0.52
La	0.0070±0.0016	0.0052±0.0008	0.355	>0.05	0.74
Li	0.0132±0.0019	0.0103±0.0022	0.361	>0.05	0.78
Mg	21.3±2.1	15.3±1.5	0.026*	<0.01*	0.60
Mn	0.151±0.039	0.091±0.012	0.155	>0.05	0.60
Nb	0.0085±0.0014	0.013±0.006	0.421	>0.05	1.53
Ni	0.138±0.017	0.154±0.029	0.629	>0.05	1.12
Pb	1.74±0.38	2.89±1.19	0.373	>0.05	1.66
Rb	0.502±0.097	0.187±0.028	0.005*	<0.01*	0.37
Sb	0.0265±0.0064	0.0440±0.0130	0.240	>0.05	1.66
Sn	0.106±0.019	0.122±0.051	0.778	>0.05	1.15
Sr	0.579±0.103	0.442±0.049	0.242	>0.05	0.76
Ti	1.01±0.023	0.640±0.200	0.255	>0.05	0.63
W	0.100±0.054	0.060±0.030	0.535	>0.05	0.60
Zn	4.64±0.78	3.02±0.25	0.061	>0.05	0.65

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

Table 6 Correlations between age and trace element mass fractions in the in normal female breast tissue (r – coefficient of correlation)

Element	**Al**	**As**	**B**	**Ba**	**Bi**	**Cd**	**Ce**	**Cr**
r	-0.26	0.38[a]	0.15	-0.17	0.17	0.25	-0.29	-0.08
Element	**Cu**	**La**	**Li**	**Mg**	**Mn**	**Nb**	**Ni**	**Pb**
r	-0.40[a]	-0.01	0.11	-0.48[b]	-0.11	0.36	0.20	0.11
Element	**Rb**	**Sb**	**Sn**	**Sr**	**Ti**	**W**	**Zn**	
r	-0.28[a]	0.27	0.05	-0.04	-0.39	-0.21	-0.09	

Significant values: [a]$p<0.05$. [b]$p<0.01$.

Table 6 shows values of the Pearson correlation coefficient between age and TE mass fraction.

4. Discussion

Acceptable agreement between the certified mass fractionation values of Ag, 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, Sm, Sn, Sr, Ti, Tl, U, V, W, Y, and Zn and those found in the present work can be seen in Table 1, which testified to the sufficient accuracy of the method used.

The Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mg, Mn, Nb, Ni, Pb, Rb, Sb, Sn, Sr, Ti, W, and Zn mass fractions were determined in all or in most of the samples, therefore, for these TE, the mean value of the mass fraction (M), standard deviation (SD), standard error of the mean (SEM), minimum, maximum, median, and percentiles with levels of 0.025 and 0.0975 was calculated for two age groups (Tables 2 and 3). The values of M, SD, and SEM can be used to compare data for different groups of samples only under the condition of a normal distribution of determining the TE mass fractions in the samples under study. Statistically reliable identification of the law of distribution of results requires large sample sizes, usually several hundred samples, and therefore is rarely used in biomedical research. In the conducted study, we could not prove or disprove the “normality” of the distribution of the results obtained due to the insufficient number of samples studied. Therefore, in addition to the M, SD, and SEM values, statistical characteristics as the median, range (minimum-maximum) and percentiles with the level of 0.025 and 0.0975 were calculated, which are valid for any law of distribution of the results of TE in breast tissue.

Most often, in studies about TE in the mammary gland, samples of visually intact tissue adjacent to the tumor are used. However, we have previously shown that the intact tissue adjacent to the thyroid tumors in terms of the level of TE content is not identical to the normal thyroid gland tissue of apparently healthy individuals [53,54]. Therefore, in our review of reported data, only results obtained from the study of normal mammary glands of apparently healthy women were used. The results obtained for Al, B, Bi, Cd, Ce, La, Ni, Sb, Sn, Sr, and Zn were in good agreement with the medians of previously published means of TE mass fractions (Table 4), whereas Ba, Cr, Cu, Mg, Mn, Nb, Pb and Rb mass fractions were within the reported ranges of means. At the same time, the As mean was below the reported mean mass fractions, while the Ti mean was higher. Reported data on Li and W were not found (Table 4). However, it should be noted that the variations of published mean values for some of the studied TE are very large and amounts to several mathematical orders (Table 4).

To assess the effect of age on the mass fractions of TE in the normal mammary gland of healthy women, two age groups described above were studied (Table 5). In normal mammary glands the mass fractions of almost all studied TE decreases with the age, except for As, Cd, Nb, Pb, Sb, and Sn. However, the increase was statistically significant only for As, while the decrease was only for Cu, Mg, and Rb. Thus, for the age group of 41-60 years, the mean Cu, Mg, and Rb mass fractions were 26%, 40%, and 63%, respectively, lower than for the age group 16-40 years (Table 5). In contrast to this, the As mass fraction for the age group of 41-60 years was two times higher ($p<0.01$) than for the age group of 16-40 years. The Pearson correlation coefficients between age and TE mass fractions confirmed these findings (Table 6).

The female breast is made up of mammary glands (glandular tissue) as well as stroma (adipose tissue and ligaments, surrounding ducts and lobules, blood, and lymph vessels) [2]. Previously it was shown that the concentration of many TE in adipose tissue is significantly lower than in epithelial tissue [55]. It is known that morphological changes, occur in the mammary gland with age, expressed in the loss of both epithelial and adipose tissue, but the relative rates of mass loss of these components have not been measured [56,57]. If the rate of loss of the relative mass of epithelial tissue is higher than that of adipose tissue, this may be one of the reasons for the decline of some TE in the mammary gland with age increase. Of particular interest is age-related increase of As mass fraction found in the breast tissue in the present study. This phenomenon can also be associated with age-related changes in the ratio of glandular and adipose tissue, if As predominantly accumulates in adipose tissue. However, all these issues require furthermore detailed study.

5. Conclusion

The analysis using ICP-MS allowed obtaining reliable quantitative data on the Al, As, B, Ba, Bi, Cd, Ce, Cr, Cu, La, Li, Mg, Mn, Nb, Ni, Pb, Rb, Sb, Sn, Sr, Ti, W, and Zn mass fractions in breast tissue samples. An important advantage of the method employed is the possibility of determining the TE mass fractions in samples weighing only a few milligrams, which makes it possible to use materials from puncture tissue biopsies for analysis.

Using the parametric Student's t-test and the non-parametric Wilcoxon-Mann-Whitney U-test to compare two age groups, as well as Pearson's correlation coefficients between age and TE mass fractions, it was found that the Cu, Mg, and Rb mass fractions in normal breast tissue decrease with age, while the As mass fraction increases. The phenomenon of the age-related changes of these TE mass fractions in the normal mammary gland, discovered for the first time, requires further detailed study.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declares that he has no competing interests.

Statement of ethical approval

All studies were approved by the Ethical Committees of the Medical Radiological Research Centre (MRRC), 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.

Authors' contribution

All authors contributed to the study conception and design. The first draft of the manuscript was written by Vladimir Zaichick and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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