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Prostatic Tissue Levels of 43 Trace Elements in Patients with Prostate Adenocarcinoma

Vladimir Zaichick[1] & Sofia Zaichick[2]

[1] Medical Radiological Research Center, Obninsk, Russia

[2] Department of Medicine, University of Illinois College of Medicine, Chicago, USA

Correspondence: Vladimir Zaichick, Medical Radiological Research Center, Obninsk 249036, Russia. Tel: 7-48439-60289. E-mail: vezai@obninsk.com

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Abstract

Adenocarcinoma of prostate gland is an internationally important health problem in men, particularly in developed countries. The aim of this exploratory study was to evaluate whether significant changes in the prostatic tissue levels of trace elements exist in the malignantly transformed prostate. Prostatic tissue levels of 43 trace elements were prospectively evaluated in 36 patients with prostate adenocarcinoma and 37 healthy males. Measurements were performed using a combination of non-destructive and destructive methods: instrumental neutron activation analysis and inductively coupled plasma mass spectrometry, respectively. Tissue samples were divided into two portions. One was used for morphological study while the other was intended for trace element analysis. The reliability of difference in the results between normal and cancerous prostate tissues was evaluated by Student's t-test. It was found that the contents of Ag, Al, Au, B, Be, Br, Ce, Cr, Dy, Er, Fe, Gd, Hg, Li, Mn, Nd, Ni, Pr, Sb, Sn, Th, Tl, Y, and Zr were significantly higher while those of Cd, Co, Rb, Sc, Se, and Zn were significantly lower in cancerous tissues than in normal tissues. Moreover, it was shown that malignant transformation significantly changed the relationships of trace elements in prostate. Thus, in adenocarcinoma transformed prostate tissue the trace element metabolism is significantly disturbed.

Keywords: Chemical elements, human prostate gland, adenocarcinoma, neutron activation analysis, inductively coupled plasma mass spectrometry

1. Introduction

Prostate cancer (PCa) is the most prevalent nonskin male cancer in many populations, including the United States, West European states, Australia, New Zealand, and others (Rebbeck & Haas, 2014). PCa ranks second in incidence and the fifth in mortality in men worldwide (Ferlay et al., 2015). Although the etiology of PCa is unknown, several risk factors including diet (calcium, zinc and some other nutrients) have been well identified (Rebbeck, 2006; Aslam & Neubauer, 2013). It is also reported that the risk of having PCa drastically increases with age, being three orders of magnitude higher for the age group 40–79 years than for those younger than 40 years (Jemal et al., 2003; Rebbeck, 2006).

Trace elements have essential physiological functions such as maintenance and regulation of cell function, gene regulation, activation or inhibition of enzymatic reactions, and regulation of membrane function. Essential or toxic (mutagenic, carcinogenic) properties of trace elements depend on tissue-specific need or tolerance, respectively (Zaichick, 2006). Excessive accumulation or an imbalance of the chemical elements may disturb the cell functions and may result in cellular degeneration or death (Ektessabi et al., 2001; Yoshida et al., 2001; Zaichick, 2006).

High zinc (Zn) concentrations in prostate tissue are probably one of the main factors acting in both initiation and promotion stages of prostate carcinogenesis (Isaacs, 1983; V. Zaichick & S. Zaichick, 1999, 2014; V. Zaichick, 2004). A significant tendency of age-related increase in Zn, and many other trace element mass fractions in the normal prostate was recently demonstrated by us (S. Zaichick & V. Zaichick, 2010, 2011, 2011a, 2011b; S. Zaichick et al., 2012a; V. Zaichick et al., 2012b; V. Zaichick & S. Zaichick, 2013, 2013a, 2013b, 2013c, 2014a, 2014b, 2014c, 2014d; Zaichick, 2015). Moreover, it was found an androgen dependence of the prostatic tissue levels of some trace elements, including Zn (V. Zaichick & S. Zaichick, 2013, 2013a, 2013b, 2013c, 2014d).

Thus, it seems fair to suppose that besides Zn, many other trace elements, which the prostatic tissue contents increase with age, also play a role in the pathophysiology of the prostate.

The trace element contents in tissue of the normal and cancerous prostate have been studied, producing contradictory results (Tipton et al., 1954; Koch & Smith, 1956; Stitch, 1957; Tipton & Cook, 1963; Sangen, 1967; Weinig & Zink, 1967; Liebscher & Smith, 1968; Höffken & Rausch-Stroomann, 1969; Soman et al., 1970; Forssen, 1972; Dhar et al., 1973; Kubo et al., 1976; Jafa et al., 1980; Ogunlewe & Osegbe, 1989; Oldereid et al., 1993; Banaś et al., 2001; Kwiatek et al., 2001; Paluszkiewicz, & Kwiatek, 2001; Kwiatek et al., 2004; Eckhert, 2005; Galván-Bobadilla et al., 2005; Kwiatek et al., 2005; Yaman et al., 2005; Guntupalli et al., 2007; Muecke et al., 2009; Kiziler et al., 2010; Schöpfer et al., 2010; Guzel et al., 2012; Leitão et al., 2014; Neslund-Dudas et al., 2014). The majority of these data are based on measurements of processed tissue and in many studies tissue samples are digested before analysis. The most frequently used digestion procedures have been the traditional dry ashing and wet digestion that allow destruction of organic matter of the sample. Moreover, in some cases before digestion, prostate samples are treated with solvents (distilled water, ethanol etc) and then are dried at a high temperature for many hours. Sample pretreatment and digestion is a critical step in elemental analysis, due to risk of contamination and analytes loss, contributing for the uncontrolled analysis errors (Fuente & Juarez, 1995; Zachariadis et al., 1995; Zaichick, 1997; V. Zaichick & S. Zaichick, 1997; Zaichick, 2004a; Khan et al., 2013). Additionally, only a few of these studies employed quality control using certified reference materials for determination of accuracy and precision of the trace element mass fraction measurement. Thus, the questions about the differences between trace element contents in normal and cancerous prostate tissue remained open.

It is obvious that the most accurate will be non-destructive analytical methods because they involve a minimal treatment of sample since the chances of significant loss or contamination would be decreased. During the last decades there is agreement on the absolute necessity of quality insurance in analytical research works. Therefore, this work had two aims. The first was to obtain reliable results about the trace element mass fractions and their relationships in prostate adenocarcinomas and prostates of healthy men aged over 40 years combining, in consecutive order, non-destructive instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides (INAA-LLR) with destructive inductively coupled plasma mass spectrometry (ICP-MS). The second aim was to compare the levels of trace elements studied in the malignant prostate with those in normal gland.

2. Materials and Methods

2.1 Patients and Sampling Procedure

All patients suffered from adenocarcinoma of prostate (n=36, mean age M±SD was 64±11 years, range 40-79) were hospitalized in the Urological Department of the Medical Radiological Research Centre. Transrectal puncture biopsy of suspicious indurated regions of the prostate was performed for every patient, to permit morphological study of prostatic tissue at these sites and to estimate their chemical element contents. In all cases the diagnosis adenocarcinoma has been confirmed by clinical and morphological results obtained during studies of biopsy and resected materials.

Normal prostates for the control group samples were removed at necropsy from 37 men (mean age 55±11 years, range 41-87), who had died suddenly. The majority of deaths were due to trauma. A histological examination in the control group was used to control the age norm conformity, as well as to confirm the absence of microadenomatosis and latent cancer.

2.2 Sample Preparation

All tissue samples were divided into two portions. One was used for morphological study while the other was intended for trace element analysis. After the samples intended for trace element analysis were weighed, they were freeze-dried and homogenized. The sample weighing about 10 mg (for biopsy materials) and 50 mg (for resected materials) was used for chemical element measurement by instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides (INAA-LLR). The samples for INAA-LLR were wrapped separately in a high-purity aluminum foil washed with double rectified alcohol beforehand and placed in a nitric acid-washed quartz ampoule.

After NAA-LLR investigation the prostate samples were taken out and used for ICP-MS. The samples were decomposed in autoclaves; 1.5 mL of concentrated HNO_3 (nitric acid at 65 %, maximum (max) of 0.0000005 % Hg; GR, ISO, Merck) and 0.3 mL of H_2O_2 (pure for analysis) were added to prostate tissue samples, placed in one-chamber autoclaves (Ancon-AT2, Ltd., Russia) and then heated for 3 h at 160–200 °C. After autoclaving, they were cooled to room temperature and solutions from the decomposed samples were diluted with deionized

water (up to 20 mL) and transferred to plastic measuring bottles. Simultaneously, the same procedure was performed in autoclaves without tissue samples (only HNO_3+H_2O_2+ deionized water), and the resultant solutions were used as control samples.

2.3 Certified Rreference Materials

For quality control, ten subsamples of the certified reference materials IAEA H-4 Animal muscle from the International Atomic Energy Agency (IAEA), and also five sub-samples INCT-SBF-4 Soya Bean Flour, INCT-TL-1 Tea Leaves and INCT-MPH-2 Mixed Polish Herbs from the Institute of Nuclear Chemistry and Technology (INCT, Warsaw, Poland) were analyzed simultaneously with the investigated prostate tissue samples. All samples of CRM were treated in the same way as the prostate tissue samples. Detailed results of this quality assurance program were presented in earlier publications (Zaichick & Zaichick, 2011b; Zaichick & Zaichick, 2012a).

2.4 Analytical Procedures

A vertical channel of a nuclear reactor was applied to determine the trace element mass fractions by NAA-LLR. The quartz ampoule with prostate samples and certified reference materials was soldered, positioned in a transport aluminum container and exposed to a 24-hour neutron irradiation in a vertical channel with a neutron flux of $1.3 \cdot 10^{13}$ $n \cdot cm^{-2} \cdot s^{-1}$. Ten days after irradiation samples were reweighed and repacked. The samples were measured for period from 10 to 30 days after irradiation. The duration of measurements was from 20 min to 10 hours subject to pulse counting rate. The gamma spectrometer included the 100 cm^3 Ge(Li) detector and on-line computer-based multichannel analyzer. The spectrometer provided a resolution of 1.9 keV on the ^{60}Co 1332 keV line.

An ICP-MS Thermo-Fisher "X-7" Spectrometer (Thermo Electron, USA) was used to determine the content of trace elements by ICP-MS. The element concentrations in aqueous solutions were determined by the quantitative method using multi elemental calibration solutions ICP-MS-68A and ICP-AM-6-A produced by High-Purity Standards (Charleston, SC 29423, USA). Indium was used as an internal standard in all measurements.

Details of the analytical methods and procedures used here such as nuclear reactions, radionuclides, gamma-energies, isotopes, spectrometers, spectrometer parameters and operating conditions were presented in our earlier publications (S. Zaichick & V. Zaichick, 2011b; S. Zaichick et al., 2012a).

2.5 Computer Programs and Statistics

A dedicated computer program for INAA mode optimization was used (Korelo & Zaichick, 1993). Mean values of trace element mass fractions were taken into account in final calculation for elements measured by both INAA-LLR and ICP-MS methods. Using Microsoft Office Excel software (Microsoft, the United States) the arithmetic mean, standard deviation, and standard error of mean was calculated for trace element mass fractions. The reliability of difference in the results between normal and cancerous prostate glands was evaluated by the parametric Student's *t*-test and values of $p<0.05$ were considered to be statistically significant. For the estimation of the Pearson correlation coefficient between different pairs of the trace element mass fractions in the normal and cancerous prostate tissue the Microsoft Office Excel software was also used.

3. Results

Arithmetic mean (M) and standard error of mean (SEM) for silver (Ag), aluminum (Al), gold (Au), boron (B), berillium (Be), bismuth (Bi), bromine (Br), cadmium (Cd), cerium (Ce), cobalt (Co), cromium (Cr), cesium (Cs), dysprosium (Dy), erbium (Er), iron (Fe), gadolinium (Gd), mercury (Hg), holmium (Ho), lanthanum (La), lithium (Li), manganese (Mn), molybdenum (Mo), niobium (Nb), neodymium (Nd), nickel (Ni), lead (Pb), praseodymium (Pr), rubidium (Rb), antimony (Sb), scandium (Sc), selenium (Se), samarium (Sm), tin (Sn), terbium (Tb), thorium (Th), titanium (TI), thallium (Tl), thulium (Tm), uranium (U), yttrium (Y), ytterbium (Yb), Zn and zirconium (Zr) mass fraction in cancerous (group of patients with prostate adenocarcinoma) and normal (age-matched control group) prostate tissue are presented in Table 1. This table also depicts the ratios of means and the reliability of difference between mean values of trace element mass fractions in cancerous and normal prostate tissue.

The comparison of this work results with other published information for Ag, Al, Au, B, Be, Bi, Br, Cd, Ce, Co, Cr, Cs, Dy, Er, Fe, Gd, Hg, Ho, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Sn, Tb, Th, Ti, Tl, Tm, U, Y, Yb, Zn and Zr mass fraction in normal and cancerous prostate glands of adult males is shown in Tables 2 and 3, respectively. When our results were compared with data of literature a number of values for trace element mass fractions were not expressed on a dry mass basis by the authors of the cited references. However, we calculated these values using the medians of published data for water – 83% and ash – 1% (on wet mass basis)

contents in nonhyperplastic prostate of adult men (Woodard & White, 1986; Saltzman et al., 1990), and also for water – 80% in prostate cancer tissue (Györkey et al., 1967).

The data of inter-correlation calculations (values of *r* – coefficient of correlation) including pairs of selected Al, Bi, Cd, Co, Fe, Mn, Sb, Se, Sn, and Zn mass fraction with all other trace element mass fractions identified by us in normal and cancerous prostate glands are presented in Tables 4 and 5 respectively.

Table 1. Comparison of mean values (M±SEM) of the trace element mass fraction (mg/kg, dry mass basis) in normal and cancerous prostate tissue

Element	Prostatic tissue			Ratio
	Adenocarcinoma 40-79 year n=36	Normal 41-87 year n=37	Student's t-test $p \leq$	Adenocarcinoma to Normal
Ag	0.294±0.043	0.038±0.006	0.000015	7.71
Al	353±96	34.2±3.5	0.016	10.3
Au	0.0353±0.0071	0.0041±0.0008	0.0046	8.61
B	16.4±5.6	1.04±0.18	0.040	15.8
Be	0.01643±0.00237	0.00094±0.00007	0.00061	17.5
Bi	1.89±0.32	0.029±0.011	0.0012	65.2
Br	95.5±10.8	27.9±2.9	0.000049	3.42
Cd	0.385±0.096	1.12±0.13	0.000088	0.34
Ce	0.1056±0.0167	0.0309±0.0050	0.0035	3.42
Co	0.0298±0.0035	0.0467±0.0064	0.025	0.64
Cr	2.15±0.45	0.56±0.08	0.0027	3.84
Cs	0.0420±0.0058	0.0339±0.0033	0.25 (NS)	1.24
Dy	0.00814±0.00120	0.00293±0.00049	0.0038	2.78
Er	0.00333±0.00046	0.00148±0.00023	0.0052	2.25
Fe	163±21	111±9	0.030	1.47
Gd	0.00910±0.00218	0.00290±0.00041	0.029	3.14
Hg	0.095±0.018	0.052±0.008	0.038	1.83
Ho	0.002046±0.000272	0.000567±0.000079	0.0012	3.61
La	0.941±0.753	0.080±0.020	0.30 (NS)	11.8
Li	0.2933±0.0770	0.0419±0.0055	0.017	7.00
Mn	7.24±2.04	1.34±0.08	0.028	5.40
Mo	0.355±0.045	0.282±0.038	0.31 (NS)	1.26
Nb	≤0.0053	0.0054±0.0012	-	≤0.98
Nd	0.0409±0.0068	0.0137±0.0021	0.0064	2.99
Ni	7.26±0.79	3.10±0.51	0.00095	2.34
Pb	2.30±0.45	2.39±0.56	0.91 (NS)	0.96
Pr	0.00867±0.00173	0.00353±0.00053	0.025	2.46
Rb	8.2±0.8	13.3±0.9	0.000046	0.62
Sb	0.513±0.079	0.043±0.006	0.0000042	11.9
Sc	0.0112±0.0014	0.0294±0.0053	0.0031	0.38
Se	0.58±0.11	0.75±0.05	0.16 (NS)	0.77
Sm	0.0107±0.0043	0.0027±0.0004	0.12 (NS)	3.96
Sn	1.48±0.30	0.32±0.06	0.0076	4.63
Tb	≤0.0008	0.00039±0.00006	-	≤2.05
Th	0.0540±0.0176	0.0033±0.0007	0.028	16.4
Ti*	≤8.0	2.82±0.64	-	≤2.83
Tl	0.0267±0.0082	0.0014±0.0001	0.022	19.1
Tm	≤0.00052	0.00024±0.00003	-	≤2.17
U	0.0050±0.0005	0.0070±0.0021	0.37 (NS)	0.71
Y	0.0346±0.0035	0.0187±0.0043	0.0080	1.85
Yb	0.00255±0.00055	0.00141±0.00025	0.25 (NS)	1.81
Zn	122±12	1031±129	0.000000027	0.118
Zr	0.901±0.213	0.036±0.006	0.0067	25.0

M – arithmetic mean, SEM – standard error of mean, NS – not significant difference, * Titanium tools were used for sampling and sample preparation.

Table 2. Median, minimum and maximum value of means of trace element mass fractions (mg/kg, on dry mass basis) in normal prostate tissue of adult males according to data from the literature in comparison with this works' results for males aged 41-87 years

Element	Published data [Reference]			This work
	Median of means, (n^a)	Minimum of means M or M±SD, (n^b)	Maximum of means M or M±SD, (n^b)	M±SD n=37
Ag	0.05 (5)	0.041±0.033 (64) [1]	0.24 (7) [2]	0.038±0.030
Al	34.2 (6)	13±66 (50) [3]	47 (9) [4]	34±18
Au	<0.7 (3)	0.0039±0.0041 (64) [1]	1.5 (3 [2]	0.0041±0.0035
B	0.97 (5)	<0.47 (50) [3]	1.2 (1) [2]	1.04±0.86
Be	0.0010 (1)	0.0010±0.0004 (64) [1]	0.0010±0.0004 (64) [1]	0.00094±0.00035
Bi	<0.055 (2)	0.021±0.048 (64) [1]	<0.09 (50) [3]	0.029±0.056
Br	27.0 (8)	14±9 (4) [5]	35.5±30.2 (64) [6]	28±15
Cd	0.79 (21)	0.07 (129) [7]	427 ±497 (55) [8]	1.12±0.64
Ce	0.028 (1)	0.028±0.024 (64) [1]	0.028±0.024 (64) [1]	0.031±0.024
Co	<0.063 (6)	0.022±0.010 (16) [9]	12 (9) [4]	0.047±0.035
Cr	≤0.64 (9)	0.042 (50) [3]	29.4 (5) [10]	0.56±0.43
Cs	0.071 (3)	0.034±0.015 (64) [1]	2.8 (12) [11]	0.034±0.017
Dy	0.0031 (1)	0.0031±0.0032 (64) [1]	0.0031±0.0032 (64) [1]	0.0029±0.0024
Er	0.0018 (1)	0.0018±0.0022 (64) [1]	0.0018±0.0022 (64) [1]	0.0015±0.0011
Fe	147 (21)	5.7±0.1 (5) [12]	1040±65 (10) [13]	111±51
Gd	0.0030 (1)	0.0030±0.0030 (64) [1]	0.0030±0.0030 (64) [1]	0.0029±0.0020
Hg	0.035 (3)	0.024±0.014 (16) [9]	0.65±0.58 (5) [14]	0.052±0.043
Ho	0.0056 (1)	0.0056±0.0049 (64) [1]	0.0056±0.0049 (64) [1]	0.00057±0.00040
La	0.074 (1)	0.074±0.094 (64[1]	0.074±0.094 (64) [1]	0.080±0.099
Li	0.040 (3)	0.040±0.024 (64) [1]	0.040±0.027 (16) [21]	0.042±0.026
Mn	1.52 (15)	<0.47 (12) [11]	7.25±5.00 (4) [10]	1.34±0.40
Mo	2.8 (6)	0.14 (4) [3]	1.8 (2) [2]	0.28±0.19
Nb	0.0051 (1)	0.0051±0.0052 (64) [1]	0.0051±0.0052 (64) [1]	0.0054±0.0058
Nd	0.013 (1)	0.013±0.011 (64) [1]	0.013±0.011 (64) [1]	0.014±0.010
Ni	<0.47 (4)	0.14 (4) [15]	14.1 (27) [16]	3.10±2.49
Pb	1.2 (12)	0.15 (41) [17]	9.4 (4) [18]	2.39±2.85
Pr	0.0033 (1)	0.0033±0.0027 (64) [1]	0.0033±0.0027 (64) [1]	0.0035±0.0026
Rb	15.9 (7)	4.7 (9) [4]	58±33 (4) [18]	13.3±5.1
Sb	0.051 (4)	0.040±0.037 (64) [1]	0.42±0.56 (7) [14]	0.043±0.036
Sc	0.015 (2)	0.0093±0.0046 (16) [9]	0.020±0.020 (64) [16]	0.029±0.023
Se	0.91 (17)	0.32 (129) [7]	18.8±2.4 (27) [16]	0.75±0.27
Sm	0.0027 (1)	0.0027±0.0024 (64) [1]	0.0027±0.0024 (64) [1]	0.0027±0.0018
Sn	3.3 (5)	0.25±0.28 (64) [1]	4.4 (7) [2]	0.32±0.32
Tb	0.0004 (1)	0.0004±0.0005 (64) [1]	0.0004±0.0005 (64) [1]	0.00039±0.00030
Th	0.0024 (1)	0.0024±0.0030 (64) [1]	0.0024±0.0030 (64) [1]	0.0033±0.0036
Ti	8.9 (6)	<0.24 (50) [3]	156±9 (27) [16]	2.8±3.1*
Tl	0.0014 (3)	0.0014 (1) [19]	0.59 (1) [2]	0.0014±0.0007
Tm	0.0003 (1)	0.0003±0.0004 (64) [1]	0.0003±0.0004 (64) [1]	0.00024±0.00017
U	0.2 (2)	0.0049±0.0083 (64) [1]	0.4 (1) [20]	0.0070±0.0105
Y	46 (3)	0.019±0.021 (64) [1]	89 (12) [11]	0.019±0.021
Yb	0.0015 (1)	0.0015±0.0015 (64) [1]	0.0015±0.0015 (64) [1]	0.0014±0.0012
Zn	503 (62)	101 (1) [21]	3218 (10) [13]	1031±782
Zr	0.044 (1)	0.044±0.052 (64) [1]	0.044±0.052 (64) [1]	0.036±0.027

Reference: [1] Zaichick et al., 2012a; [2] Tipton et al., 1954; [3] Tipton & Cook, 1963; [4] Stitch, 1957; [5] Kubo et al., 1976; [6] Zaichick & Zaichick, 2011; [7] Schöpfer et al., 2010; [8] Ogunlewe & Osegbe, 1989; [9] Zaichick & Zaichick, 2013a; [10] Banaś et al., 2001; [11] Forssen, 1972; [12] Sangen, 1967; [13] Jafa et al., 1980; [14] Liebscher & Smith, 1968; [15] Koch & Smith, 1956; [16] Guntupalli et al., 2007; [17] Olderei et al., 1993; [18] Soman et al., 1970; [19] Weinig & Zink, 1967; [20] Höffken & Rausch-Stroomann, 1969; [21] Galván-Bobadilla et al., 2005. M – arithmetic mean, SD – standard deviation, n^a – No. of references contribution to this value, n^b – No. of samples, * Titanium tools were used for sampling and sample preparation.

Table 3. Median, minimum and maximum value of means of trace element mass fractions (mg/kg, on dry mass basis) in cancerous prostate tissue according to data from the literature in comparison with this works' result

Element	Published data [Reference]			This work
	Median of means, (n^a)	Minimum of means M or M±SD, (n^b)	Maximum of means M or M±SD, (n^b)	M±SD n=36
Ag	-	-	-	0.294±0.043
Al	-	-	-	353±255
Au	-	-	-	0.0353±0.0071
B	1.78 (1)	1.78±0.65 (23) [1]	1.78±0.65 (23) [1]	16.4±13.6
Be	-	-	-	0.0164±0.0063
Bi	-	-	-	1.89±0.86
Br	1.5 (1)	1.5±6.0 (27) [2]	1.5±6.0 (27) [2]	95.5±37.5
Cd	1.0 (17)	0.22 (21) [3]	3248±145 (12) [4]	0.385±0.253
Ce	-	-	-	0.106±0.044
Co	25 (1)	23.5± 2.0 (4) [5]	27± 3 ((4) [5]	0.0298±0.0144
Cr	7 (4)	1.65± 0.30 (4) [5]	217±8 ((27) [2]	2.15±1.84
Cs	-	-	-	0.042±0.015
Dy	-	-	-	0.0081±0.0032
Er	-	-	-	0.00333±0.00046
Fe	195 (15)	12.5±5.0 (20) [6]	6850 (1) [7]	163±106
Gd	-	-	-	0.0091±0.0058
Hg	-	-	-	0.095±0.074
Ho	-	-	-	0.00205±0.00072
La	-	-	-	0.94±1.84
Li	-	-	-	0.293±0.204
Mn	17.3 (6)	8.0±2.0 (3) [8]	160±22 (5) [9]	7.24±5.40
Mo	-	-	-	0.355±0.064
Nb	-	-	-	≤0.0053
Nd	-	-	-	0.041±0.018
Ni	28.5 (3)	2.35±1.55 (11) [10]	122±15 (27) [2]	7.26±2.10
Pb	0.176 (2)	0.156 (21) [3]	170±50 (23) [11]	2.30±1.20
Pr	-	-	-	0.0087±0.0046
Rb	8 (1)	8±1 (12) [12]	8±1 (12) [12]	8.18±4.31
Sb	-	-	-	0.51±0.38
Sc	-	-	-	0.0112±0.0059
Se	1.47 (15)	0.835±0.410 (17) [13]	11.5±3.5 (3) [8]	0.58±0.45
Sm	-	-	-	0.0107±0.0115
Sn	-	-	-	1.48±0.79
Tb	-	-	-	≤0.0008
Th	-	-	-	0.054±0.047
Ti	26.2 (3)	~1 (1) [14]	257±21 (27) [2]	≤8.0*
Tl	-	-	-	0.027±0.022
Tm	-	-	-	≤0.00052
U	-	-	-	0.0050±0.0014
Y	-	-	-	0.0346±0.0093
Yb	-	-	-	0.00255±0.00078
Zn	200 (44)	16.7±3.5 (3) [8]	840±85 (13) [15]	122±70
Zr	-	-	-	0.90±0.56

Reference: [1] Eckhert, 2005; {2] Guntupalli et al., 2007; [3] Neslund-Dudas et al., 2014; [4] Ogunlewe & Osegbe, 1989; [5] Kwiatek et al., 2005; [6] Kiziler et al., 2010; [7] Paluszkiewicz & Kwiatek, 2001; [8] Kiziler et al., 2004; [9] Banaś et al., 2001; [10] Yaman et al., 2005; [11] Guzel et al., 2012; [12] Leitão et al., 2014; [13] Muecke et al., 2009; [14] Kwiatek et al., 2001; [15] Dhar et al., 1973. M – arithmetic mean, SD – standard deviation, n^a – No. of references contribution to this value, n^b – No. of samples, * Titanium tools were used for sampling and sample preparation, "–" no data available.

Table 4. Intercorrelations of Al, Bi, Cd, Co, Fe, Mn, Sb, Se, Sn, and Zn mass fraction with other trace element mass fractions determined in normal prostate tissue (r – coefficient of correlation)

Element	Al	Bi	Cd	Co	Fe	Mn	Sb	Se	Sn	Zn
Ag	0.19	-0.19	-0.26	-0.08	-0.19	0.12	0.22	-0.19	0.45	0.12
Al	**1.00**	-0.09	-0.21	0.39	0.02	0.21	0.06	-0.03	-0.11	-0.14
Au	0.06	-0.18	-0.08	0.01	0.10	-0.10	0.33	0.34	0.18	-0.18
B	-0.31	0.10	0.48	0.07	0.03	0.09	-0.09	-0.12	0.13	-0.15
Be	0.65[b]	0.14	-0.21	0.80[b]	0.01	-0.01	-0.28	-0.27	-0.05	0.20
Bi	-0.09	**1.00**	0.09	0.14	0.21	-0.03	-0.28	-0.01	0.05	-0.08
Br	0.19	-0.41	0.16	-0.21	-0.12	-0.09	0.26	-0.23	0.29	-0.28
Cd	-0.21	0.09	**1.00**	-0.14	0.35	-0.09	-0.16	-0.11	-0.05	-0.27
Ce	0.39	0.65[b]	-0.01	0.44	0.29	0.11	-0.22	-0.05	-0.09	-0.20
Co	0.39	0.14	-0.14	**1.00**	0.25	-0.04	0.18	-0.07	0.01	-0.09
Cr	-0.04	-0.26	0.29	0.12	0.42	-0.01	0.26	0.42	-0.21	0.03
Cs	-0.29	0.16	-0.24	-0.21	-0.30	0.01	0.07	0.32	0.08	0.14
Dy	0.88[b]	-0.03	-0.27	0.62[a]	-0.14	0.21	-0.11	-0.13	-0.21	-0.17
Er	0.91[b]	-0.05	-0.23	0.33	-0.09	0.24	0.01	-0.08	-0.14	-0.17
Fe	0.02	0.21	0.35	0.25	**1.00**	0.01	0.33	0.45	-0.22	0.17
Gd	0.86[b]	0.24	-0.20	0.41	-0.03	0.14	-0.09	-0.11	-0.19	-0.23
Hg	-0.09	-0.15	0.03	0.01	0.36	0.01	0.08	0.41	0.19	0.38
Ho	0.86[b]	-0.05	-0.19	0.25	0.01	0.32	0.03	-0.06	-0.18	-0.24
La	0.18	0.03	-0.17	-0.06	0.05	0.51	0.04	-0.17	0.19	-0.07
Li	0.43	-0.02	-0.05	0.41	-0.02	0.08	0.25	0.19	0.33	-0.14
Mn	0.21	-0.03	-0.09	-0.04	0.01	**1.00**	0.26	0.10	0.01	-0.04
Mo	-0.04	-0.23	-0.01	-0.11	0.04	0.17	0.32	-0.14	0.61[a]	-0.04
Nb	0.15	-0.18	-0.04	-0.05	-0.28	0.36	0.39	-0.22	0.45	-0.31
Nd	0.57[a]	0.60[a]	-0.14	0.48	0.10	0.08	-0.16	-0.06	-0.12	-0.22
Ni	-0.06	-0.21	0.09	-0.03	0.03	0.10	-0.12	-0.16	0.05	0.07
Pb	-0.13	0.23	0.26	-0.02	0.23	0.09	0.09	-0.05	0.36	-0.01
Pr	0.49	0.65[b]	-0.05	0.52	0.20	0.07	-0.21	-0.05	-0.10	-0.20
Rb	-0.07	0.13	-0.10	0.14	0.63[b]	-0.08	0.38	0.26	-0.29	0.25
Sb	0.06	-0.28	-0.16	0.18	0.33	0.26	**1.00**	-0.08	0.17	-0.09
Sc	-0.14	0.59[a]	-0.06	0.41	0.70[b]	-0.42	0.03	0.63[b]	-0.34	0.62[a]
Se	-0.03	-0.01	-0.11	-0.07	0.45	0.10	-0.08	**1.00**	-0.13	0.27
Sm	0.73[b]	0.43	-0.21	0.53[a]	-0.01	0.15	-0.08	-0.05	-0.16	-0.21
Sn	-0.11	0.05	-0.05	0.01	-0.22	0.01	-0.17	-0.13	**1.00**	-0.10
Tb	0.87[b]	0.15	-0.26	0.42	-0.08	0.16	-0.06	-0.06	-0.14	-0.22
Th	0.37	0.53[a]	-0.15	0.61[a]	-0.08	0.08	-0.19	0.04	-0.17	-0.16
Ti*	0.07	-0.01	-0.04	-0.08	0.13	0.34	-0.24	-0.12	-0.05	0.19
Tl	0.35	-0.20	-0.19	-0.16	0.24	0.31	-0.16	0.64[b]	-0.28	0.50
Tm	0.91[b]	-0.14	-0.13	0.26	-0.10	0.27	0.04	-0.10	-0.19	-0.20
U	-0.34	-0.10	-0.25	-0.08	-0.21	0.07	0.15	-0.29	0.40	0.01
Y	0.74[b]	-0.03	-0.19	0.21	-0.03	0.13	0.09	-0.21	0.37	-0.03
Yb	0.92[b]	-0.08	-0.20	0.32	-0.07	0.24	-0.03	-0.10	-0.17	-0.19
Zn	-0.14	-0.08	-0.27	-0.09	0.17	-0.04	-0.09	0.27	-0.10	**1.00**
Zr	0.60[a]	-0.19	-0.12	0.34	-0.18	0.23	-0.17	0.09	-0.31	-0.08

* Titanium tools were used for sampling and sample preparation, Significant difference: [a] - $p \leq 0.01$, [b] - $p \leq 0.001$.

4. Discussion

The INAA-LLR and ICP-MS allowed determine the mean mass fractions of 10 (Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn) and 41 (Ag, Al, Au, B, Be, Bi, Br, Cd, Ce, Co, Cr, Cs, Dy, Er, Gd, Hg, Ho, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Se, Sm, Sn, Tb, Th, Ti, Tl, Tm, U, Y, Yb, Zn and Zr) trace elements, respectively, in the tissue samples of BPH and normal prostate glands. Thus, the use in consecutive order two analytical methods allowed us to estimate the mass fractions of 43 chemical elements. In some cancerous tissue samples with low masses (biopsy materials) the mass fractions of Nb, Tb, Ti, and Tm were under detection limits (DL). The possible upper limit of the mean (≤M) for these trace elements was calculated as the average mass fraction, using the value of

the detection limit instead of the individual value when the latter was found to be below the DL:

$$\leq M = \left(\sum_{i}^{n_i} C_i + DL \cdot n_j \right) / n \quad (1)$$

where C_i is the individual value of the trace-element mass fraction in sample -*i*, n_i is 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.)

Table 5. Intercorrelations of Al, Bi, Cd, Co, Fe, Mn, Sb, Se, Sn, and Zn mass fraction with other trace element mass fractions determined in cancerous prostate tissue (*r* – coefficient of correlation)

Element	Al	Bi	Cd	Co	Fe	Mn	Sb	Se	Sn	Zn
Ag	0.56	0.72	-0.16	0.09	-0.14	0.52	0.06	-0.16	0.61	-0.18
Al	**1.00**	0.64	-0.01	0.14	-0.40	0.61	0.04	-0.57	0.87[b]	-0.41
Au	0.15	0.59	-0.28	0.46	-0.46	0.84[a]	0.11	0.08	0.92[b]	-0.54
B	0.70	0.41	0.25	0.99[b]	-0.53	0.08	0.09	-0.51	0.45	-0.13
Be	0.80[a]	0.63	-0.33	-0.13	-0.33	0.64	0.07	-0.17	0.97[b]	-0.58
Bi	0.64	**1.00**	-0.58	-0.97[b]	-0.12	0.51	0.23	-0.95[b]	0.71	-0.76[a]
Br	0.36	0.65	-0.57	0.24	0.19	0.21	-0.19	-0.60	0.48	0.01
Cd	-0.01	-0.58	**1.00**	0.85[b]	-0.14	-0.29	-0.14	0.87[b]	-0.30	0.81[a]
Ce	0.69	0.38	-0.32	0.49	-0.54	0.85[b]	-0.03	0.19	0.80[a]	-0.53
Co	0.14	-0.97[b]	0.85[b]	**1.00**	0.08	0.94[b]	-0.27	0.59	0.28	0.45
Cr	0.75[a]	0.66	-0.46	0.09	0.29	0.25	0.15	-0.04	0.60	0.09
Cs	0.63	0.80[b]	-0.32	-0.64	0.06	0.60	0.23	-0.76[a]	0.69	-0.39
Dy	0.76[a]	0.64	-0.28	-0.98[b]	-0.27	0.54	-0.13	-0.28	0.88[b]	-0.49
Er	0.78[a]	0.67	-0.19	-0.53	-0.08	0.66	0.22	-0.33	0.88[b]	-0.34
Fe	-0.40	-0.12	-0.14	0.08	**1.00**	-0.42	-0.01	-0.14	-0.43	-0.03
Gd	0.82[a]	0.57	-0.22	0.07	-0.35	0.83[a]	-0.29	-0.50	0.77[a]	-0.44
Hg	0.77[a]	0.32	-0.19	0.41	-0.14	0.90[b]	0.17	0.42	0.86[b]	0.19
Ho	0.22	-0.10	-0.15	0.21	-0.31	0.16	-0.09	0.39	0.38	-0.31
La	-0.39	-0.43	-0.10	0.25	-0.26	-0.42	-0.34	0.19	-0.35	-0.13
Li	0.91[b]	0.62	-0.02	0.47	-0.41	0.69	0.07	-0.41	0.87[b]	-0.37
Mn	0.61	0.51	-0.29	0.94[b]	-0.42	**1.00**	-0.10	-0.10	0.75[a]	-0.43
Mo	-0.10	0.10	-0.66	-0.37	0.05	-0.29	-0.18	-0.24	0.35	-0.57
Nb	-	-	-	-	-	-	-	-	-	-
Nd	0.90[b]	0.52	-0.12	0.99[b]	-0.40	0.64	-0.10	-0.27	0.85[b]	-0.44
Ni	0.73	0.48	-0.38	-0.99[b]	-0.03	0.66	-0.01	-0.80[a]	0.75[a]	-0.42
Pb	0.13	-0.19	-0.01	0.21	-0.28	0.07	-0.23	0.41	0.25	-0.17
Pr	0.82[a]	0.55	-0.14	0.27	-0.35	0.60	0.07	-0.45	0.73	-0.42
Rb	-0.54	-0.88[b]	0.73	0.39	0.25	-0.39	-0.31	0.66	-0.60	0.38
Sb	0.04	0.23	-0.14	-0.27	-0.01	-0.10	**1.00**	-0.27	0.06	-0.27
Sc	0.38	0.96[b]	-0.47	0.39	0.08	-0.63	-0.29	0.29	-0.73	0.24
Se	-0.57	-0.95[b]	0.87[b]	0.59	-0.14	-0.10	-0.27	**1.00**	-0.40	0.70
Sm	0.26	0.33	-0.34	0.56	-0.17	0.16	0.63	-0.05	0.48	-0.36
Sn	0.87[b]	0.71	-0.30	0.28	-0.43	0.75[a]	0.06	-0.40	**1.00**	-0.60
Tb	-	-	-	-	-	-	-	-	-	-
Th	0.92[b]	0.54	0.06	0.89[b]	-0.46	0.66	0.06	-0.31	0.76[a]	-0.35
Ti*	-	-	-	-	-	-	-	-	-	-
Tl	0.79[a]	0.55	0.15	0.99[b]	-0.45	0.35	0.24	-0.17	0.72	-0.30
Tm	-	-	-	-	-	-	-	-	-	-
U	0.18	0.17	-0.19	0.54	-0.33	0.08	-0.28	-0.24	0.13	-0.30
Y	0.83[a]	0.57	-0.29	-0.96[b]	-0.27	0.60	0.04	-0.60	0.87[b]	-0.49
Yb	-0.78[a]	-0.25	0.02	-0.99[b]	0.93[b]	-0.85[b]	-0.49	-0.06	-0.78[a]	0.47
Zn	-0.41	-0.76[a]	0.81[a]	0.45	-0.03	-0.43	-0.27	0.70	-0.60	**1.00**
Zr	-0.18	-0.10	0.26	0.71	-0.21	0.05	0.49	0.04	-0.31	0.16

* Titanium tools were used for sampling and sample preparation, Significant difference: [a] - $p \leq 0.01$, [b] - $p \leq 0.001$.

A good agreement was found between the mean values of the Ag, Co, Cr, Hg, Rb, Sb, Se, and Zn mass fractions determined by both INAA-LLR and ICP-MS indicating complete digestion of the prostate tissue samples (for ICP-MS techniques) and correctness of all results obtained by the two methods. The fact that the elemental mass fractions (M±SD) of the certified reference materials obtained in the present work were in good agreement with the certified values and within the corresponding 95 % confidence intervals (Zaichick & Zaichick, 2011b; Zaichick & Zaichick, 2012a) suggests an acceptable accuracy of the measurements performed on the prostate tissue samples.

In the cancerous prostates, we have observed a significant increase in mass fraction of Ag, Al, Au, B, Be, Bi, Br, Ce, Cr, Dy, Er, Fe, Gd, Hg, Ho, Li, Mn, Mo, Nd, Ni, Pr, Sb, Sm, Sn, Th, Tl, Y, and Zr in comparison with the histologically normal prostates (Table 1). In particular, a significant higher level of Ag (p<0.000015), Al (p<0.16), Au (p<0.0046), B (p<0.04), Be (p<0.0006), Bi (p<0.0012), Cr (p<0.0027), Li (p<0.017), Mn (p<0.028), Sb (p<0.000004), Sn (p<0.0076), Th (p<0.028), Tl (p<0.022), and Zr (p<0.0067) mass fraction was found in cancerous tissue (Table 1). For example, in prostate glands of patients with prostate adenocarcinoma the means of Ag, Al, Au, B, Be, Bi, Cr, Li, Mn, Sb, Sn, Th, Tl, and Zr mass fractions were nearly 4-65 times greater than in prostate glands of control group. Such trace elements as Ag, Al, Au, B, Be, Bi, Cr, Li, Mn, Sb, Sn, Th, Tl, and Zr binds more tightly within the prostatic cells than within prostatic fluid (V. Zaichick & S. Zaichick, 2014e, 2014f, 2014g, 2014h). Thus, because the major characteristic of malignancy is an uncontrolled cell proliferation, becomes clear why an increase in the prostatic Ag, Al, Au, B, Be, Bi, Cr, Li, Mn, Sb, Sn, Th, Tl, and Zr mass fractions has respect to the prostate adenocarcinom.

In contrary, the Zn mass fractions were almost 8 times lower, and the Cd, Co, Rb, Sc, and Se mass fractions were approximately 25-65%, lower in adenocarcinoma than in normal prostate tissue (Table 1). In our previous studies we demonstrated that the glandular lumen and, therefore, the prostatic fluid is the main pool of Zn, Se, and Rb accumulation in the normal human prostate (V. Zaichick & S. Zaichick, 2014, 2014e, 2014f, 2014g, 2014h). It was concluded that Zn, Se, and Rb are involved in functional features of prostate tissue. Because malignant transformation is accompanied by a loss of tissue-specific functional features, including the prostatic fluid production, this process leads to a significant reduction in the contents of trace elements such as Zn, Rb, and Se associated with functional characteristics of the human prostate tissue. The biochemical reason behind the low levels of Cd, Co, and Sc mass fractions in cancerous tissue requires further study for a more complete understanding.

No statistically significant differences between the mean values of all other trace element mass fractions determined in this study (Cs, La, Mo, Pb, Sm, U, and Yb) for cancerous and normal prostates were shown (Table 1).

The results for all trace element mass fractions in the prostates of the control group are in accordance with our earlier findings in prostates of apparently healthy men aged over 41 years (S. Zaichick & V. Zaichick, 2010, 2011, 2011a, 2011b; S. Zaichick et al., 2012a; V. Zaichick et al., 2012b; V. Zaichick & S. Zaichick, 2014a, 2014b, 2014c; V. Zaichick, 2015) (Table 2). The data reported by other researches and presented in Table 2 also includes samples obtained from patients who died from different non-urological diseases. Values obtained for all trace elements in this study agreed well with median of mean values or were inside ranges of means cited for the normal human prostate (Table 2).

The obtained mean values for Cd, Cr, Fe, Mn, Ni, Rb, Se, Ti, and Zn mass fractions in cancerous tissue, as shown in Table 3, agreed well with median of means cited by other researches. The means of this work for B and Br mass fractions are almost one and two orders of magnitude higher than previously reported maximal mean values, respectively, while Co mass fractions are three orders of magnitude lower than previously reported minimal mean value. No published data referring to Ag, Al, Au, Be, Bi, Ce, Cs, Dy, Er, Gd, Hg, Ho, La, Li, Mo, Nb, Nd, Pr, Sb, Sc, Sm, Sn, Tb, Th, Tl, Tm, U, Y, Yb, and Zr mass fractions in prostate cancer tissue were found.

In normal prostate glands a statistically significant (p≤0.01) direct correlation was found, for example, between the prostatic Al and Be, Al and Dy, Al and Er, Al and Gd, Al and Ho, Al and Nd, Al and Sm, Al and Tb, Al and Tm, Al and Y, Al and Yb, and also Al and Zr, between the prostatic Bi and Ce, Bi and Nd, Bi and Pr, Bi and Sc, and also Bi and Th, between the prostatic Co and Be, Co and Dy, Co and Sm, and also Co and Th, between the prostatic Fe and Rb and also Fe and Sc, between the prostatic Se and Sc, and also Se and Tl, between the prostatic Sn and Mo, and between the prostatic Zn and Sc (Table 4). The interpretation of all observed relationships of trace element mass fraction in normal prostate tissue requires further study for a more complete understanding.

In cancerous prostates some correlations between trace elements found in the control group are no longer evident,

for example, correlations for some pairs with Fe, Se, and Zn, but other correlations (direct Al-Cr, Al-Hg, Al-Li, Al-Sn, Al-Th, Al-Tl, Bi-Co, Bi-Cs, Cd-Co, Cd-Se, Cd-Zn, Co-B, Co-Mn, Co-Nd, Co-Tl, Fe-Yb, Mn-Au, Mn-Ce, Mn-Gd, Mn-Hg, Mn-Sn, Sn-Au, Sn-Be, Sn-Ce, Sn-Dy, Sn-Er, Sn-Gd, Sn-Hg, Sn-Li, Sn-Nd, Sn-Ni, Sn-Th, Sn-Y, and reverse Al-Yb, Bi-Co, Bi-Rb, Bi-Se, Bi-Zn, Co-Dy, Co-Ni, Co-Y, Co-Yb, Mn-Yb, Se-Cs, Se-Ni, Sn-Yb) are arisen (Table 5). Thus, if we accept the levels and relationships of trace element mass fraction in prostate glands of males in the control group as a norm, we have to conclude that with a malignant transformation the levels and relationships of trace elements in prostate significantly changed. No published data referring to correlations between trace elements mass fractions in cancerous prostate tissue were found.

Characteristically, elevated or deficient levels of trace elements observed in cancerous tissues are discussed in terms of their potential role in the initiation, promotion, or inhibition of prostate cancer. In our opinion, abnormal levels of Zn, Se, Rb and some other trace elements in adenocarcinoma could be the consequence of malignant transformation. On the other hand, findings of this study documented fact that the adenocarcinoma of human prostate accumulates high levels of many trace elements including Al, B, Be, Bi, Cr, Fe, Hg, Ni, Sn, Th, and Zr. Genotoxicity and carcinogenicity of these elements are well known (Anghileri et al., 2000; Gordon & Bowser, 2003; Crespo-López et al., 2009; Bian et al., 2011; Gonzalez-Vasconcellos et al., 2011; Müezzinoğlu et al., 2011; Sappino et al., 2012; Helmig et al., 2013; Adámik et al., 2015; Farasani & Darbre, 2015). On the other hand, compared to human body soft tissues, the normal prostate of young adults has higher levels of many trace elements, including Zn (V. Zaichick & S. Zaichick, 2013, 2013a, 2013b, 2013c, 2014d). Moreover, the level of Ba, Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, Th, U, Zn and some other trace elements continue to increase with age (S. Zaichick & V. Zaichick, 2011, 2011a, 2011b; S. Zaichick et al., 2012a; V. Zaichick et al., 2012b; V. Zaichick & S. Zaichick, 2014a, 2014b, 2014c; Zaichick, 2015). In our earlier publications (V. Zaichick & S. Zaichick, 1999, 2014; Zaichick, 2004) it was discussed in detail that the age-related excessive Zn level in prostatic tissue is probably one of the main factors influencing the initiation and progression of PCa. In addition to the elevated Zn level, an age-related increase and excess in Bi, Cd, Co, Cr, Fe, Hg, Pb, Sn, Th, and U mass fractions in prostatic tissue may contribute to harmful effects on the gland. There are good reasons for such speculations since many reviews and numerous papers raise the concern about toxicity and carcinogenicity of these and other metals (Sunderman, 1979; Snow, 1992; Salnikow & Zhitkovich, 2008; Toyokuni, 2009; Martinez-Zamudio & Ha, 2011; Tokar et al., 2011; Chervona et al., 2012; Tchounwou et al., 2012; Koedrith et al., 2013; Tabrez et al., 2014). Each of metals is distinct in its primary mode of action. Moreover, there are several forms of synergistic action of metals as a part of intracellular metabolism, during which several reactive intermediates and byproducts are created (Sunderman, 1979; Snow, 1992; Koedrith et al., 2013). These reactive species are capable of potent and surprisingly selective activation of stress-signaling pathways, inhibition of DNA metabolism, repair, and formation of DNA crosslinks, which are known to contribute to the development of human cancers (Snow, 1992; Salnikow & Zhitkovich, 2008; Tchounwou et al., 2012). In addition to genetic damage via both oxidative and nonoxidative (DNA adducts) mechanisms, metals can also cause significant changes in DNA methylation and histone modifications, leading to alterations in gene expression (Salnikow & Zhitkovich, 2008; Toyokuni, 2009; Tokar et al., 2011)]. In vitro and animal carcinogenic studies provided strong support for the idea that metals can also act as co-carcinogens in combination with nonmetal carcinogens (Salnikow & Zhitkovich, 2008).

Our findings show that mass fraction of Ag, Al, Au, B, Be, Bi, Br, Cd, Ce, Co, Cr, Fe, Hg, Li, Mn, Ni, Rb, Sb, Sc, Sn, Zn and some other trace elements are significantly different in most adenocarcinomas as compared to normal prostate tissues (Tables 1). Thus, it is plausible to assume that levels of these trace elements and their different combinations in prostate tissue can be used as tumor markers. However, this subjects needs in additional studies.

5. Conclusion

The combination of nondestructive INAA-LLR and destructive ICP-MS methods is a satisfactory analytical tool for the precise determination of 43 trace element mass fractions in the tissue samples of prostate adenocarcinoma and normal prostate glands. The using two methods one by one allowed precise quantitative determinations of mean mass fraction of Ag, Al, Au, B, Be, Bi, Br, Cd, Ce, Co, Cr, Cs, Dy, Er, Fe, Gd, Hg, Ho, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Sn, Tb, Th, Tl, Ti, Tm, U, Y, Yb, Zn, and Zr. It was observed that the mass fractions of all trace elements investigated in the study with the exception of Cs, La, Mo, Pb, Se, Sm, U, and Yb show significant variations in cancerous tissues when compared with normal tissues of the prostate. Moreover, it was shown that malignant transformation significantly changed the relationships of chemical elements in prostate. Thus, our finding of content and correlation between pairs of prostatic chemical element mass fractions, detailed above, indicates that there is a great disturbance of elemental metabolism in prostate malignancy. It was supposed that elevated levels of Ag, Al, Au, B, Be, Br, Ce, Cr, Dy, Er, Fe, Gd, Hg, Li, Mn, Nd, Ni, Pr, Sb, Sn, Th, Tl, Y, and Zr as well as reduced levels of Cd, Co, Rb, Sc, Se, and Zn in prostatic tissue can be used as tumor

markers. More work is indicated in larger cohorts of patients.

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