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The Comparison between the Contents and Interrelationships of 17 Chemical Elements in Normal and Cancerous Prostate Gland

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Abstract

Background: Adenocarcinoma of prostate gland is an internationally important health problem of the man, particularly in developed countries. The aim of this exploratory study was to evaluate whether significant changes in the prostatic tissue levels of chemical elements and their interrelationships exist in the malignantly transformed prostate.

Methods: Prostatic tissue levels of Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn contents were prospectively evaluated in 36 patients with prostate adenocarcinoma (aged 40 to 79 years, stage T1-T4, European-Caucasian, citizens of Moscow and Obninsk) and 37 apparently healthy male inhabitants of Moscow (aged 41 to 87 years, European-Caucasian). Measurements were performed using a combination of non-destructive and destructive methods: instrumental neutron activation analysis and inductively coupled plasma atomic emission spectrometry, respectively. Tissue samples were divided into two portions. One was used for morphological study while the other was intended for chemical element analysis. The reliability of difference in the results between normal and cancerous prostate tissues was evaluated by Student's t-test.

Results: Mean values ± standard error of means for mass fraction (mg/kg on dry mass basis) of chemical element in the prostate adenocarcinoma were: Al 353 ± 96, B 16.4 ± 5.6, Ba 29.5 ± 10.1, Br 95.5 ± 10.8, Ca 676 ± 63, Cu 18.8 ± 3.2, Fe 176 ± 20, K 8992 ± 717, Li 0.293 ± 0.077, Mg 355 ± 80, Mn 7.24 ± 2.04, Na 7784 ± 928, P 6847 ± 717, S 5230 ± 576, Si 337 ± 41, Sr 5.56 ± 0.84 and Zn 127 ± 12, respectively. The contents of Al, B, Ba, Br, Cu, Fe, Li, Mn, Si and Sr were significantly higher while those of Ca, K, Mg, Na, S and Zn were significantly lower in cancerous tissues than in normal tissues. Moreover, it was shown that malignant transformation significantly changed the interrelationships of chemical elements in prostate.

Conclusion: In adenocarcinoma transformed prostate tissue the chemical element metabolism is significantly disturbed.

Keywords: Chemical elements; Human prostate gland; Prostate adenocarcinoma; Neutron activation analysis, Inductively coupled plasma atomic emission spectrometry

Abbreviations: PCa: Prostate Cancer; INAA-SLR: Instrumental Neutron Activation Analysis with High Resolution Spectrometry of Short Lived Radio Nuclides; ICP-AES: Inductively Coupled Plasma Atomic Emission Spectrometry

Introduction

Prostate cancer (pca) is the most prevalent nonskin male cancer in many populations, including USA, West European states, Australia, New Zealand, and others [1]. Pca ranks second in incidence and the fifth in mortality in men worldwide [2]. Although the etiology of pca is unknown, several risk factors including diet (calcium, zinc and some other nutrients) have been well identified [3,4]. It is also reported that the risk of having pca drastically increase with age, being three orders of magnitude higher for the age group 40–79 years than for those younger than 39 years [4,5]. Chemical elements (major and trace) are not only building material but 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 chemical elements depend on tissue-specific need or tolerance, respectively [6]. Excessive accumulation or an imbalance of the chemical elements may disturb the cell functions and may result in cellular degeneration or death [6-8]. High intraprostatic calcium (Ca) and zinc (Zn) concentrations are probably one of the main factors acting in both initiation and promotion stages of prostate carcinogenesis [9-14]. A significant tendency of age-related increase in Ca, magnesium (Mg), Zn, and many other chemical element mass fractions in the normal prostate was recently demonstrated by us [11-23]. Moreover, it was found that the prostatic tissue content of Ca, potassium (K), Mg, sulphur (S), and Zn are an androgen dependent chemical element, but content of aluminium (Al), boron (B), barium (Ba) bromine (Br), copper (Cu), iron (Fe), lithium (Li), manganese (Mn), sodium (Na), phosphorus (P), silicon (Si) and strontium (Sr) are not bound to levels of sex hormone [24]. Thus, it seems fair to suppose that besides Ca and Zn, many other chemical elements also play a role in the pathophysiology of the prostate. The chemical element contents in tissue of the normal [13,16,25-42] and cancerous [34,36,38,43-53] prostate have been studied, producing contradictory results. 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

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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 [54-59]. Additionally, only a few of these studies employed quality control using certified reference materials for determination of the chemical element mass fractions. Thus, the questions about the differences between chemical element contents in normal and cancerous prostate tissue remained open. It is obvious that the most effective 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 Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn mass fractions and their relationships in nonhyperplastic prostate of healthy men aged over 40 years and in adenocarcinoma of prostate combining in consecutive order non-destructive instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR) with destructive inductively coupled plasma atomic emission spectrometry (ICP-AES). The second aim was to compare the levels of chemical elements studied in the malignant prostate with those in normal gland.

Material and Methods

All patients suffered from adenocarcinoma of prostate (n = 36, mean age M ± SD was 64 ± 11 years, range 40-79, stage T1-T4, European-Caucasian, citizens of Moscow and Obninsk) were hospitalized in the Urological Department of the Medical Radiological Research Centre, Obninsk (a small city in a non-industrial region 105 km south-west of Moscow). 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 prostate 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, European-Caucasian, citizens of Moscow), who had died suddenly. The majority of deaths were due to trauma. Tissue samples were collected from the peripheral zone of prostate dorsal and lateral lobes. 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.

All tissue samples were divided into two portions. One was used for morphological study while the other was intended for chemical element analysis. After the samples intended for chemical element analysis were weighed, they were freeze-dried and homogenized. The sample weighing about 10 mg (for biopsy materials) and 50-100 mg (for resected materials) was used for chemical element measurement by INAA-SLR. The samples for INAA-SLR were sealed separately in thin polyethylene films washed beforehand with acetone and rectified alcohol. The sealed samples were placed in labelled polyethylene ampoules.

After NAA-SLR investigation the prostate samples were taken out from the polyethylene ampoules and used for ICP-AES. 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 3h 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.

A horizontal channel equipped with the pneumatic rabbit system of the WWR-C research nuclear reactor was applied to determine the mass fraction of Br, Ca, K, Mg, Mn and Na by INAASLR. The neutron flux in the channel was 1.7 × 1013 n cm^{-2} s^{-1}. Ampoules with prostate samples, biological synthetic standards [60], intra laboratory-made standards, and certified reference material (CRM) were put into polyethylene rabbits and then irradiated separately for 180s. Copper foils were used to assess neutron flux. The measurement of each sample was made twice, 1 and 120 min after irradiation. The duration of the first and second measurements was 10 and 20 min, respectively. The gamma spectrometer included the 100 cm^3 Ge (Li) detector and on-line computer based MCA system. The spectrometer provided a resolution of 1.9 kev on the 60 Co 1332 kev line.

Sample aliquots were used to determine the Al, B, Ba, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr, V and Zn mass fractions by ICP-AES using the Spectrometer ICAP-61 (Thermo Jarrell Ash, USA). The determination of the trace element content in aqueous solutions was made by the quantitative method using calibration solutions (High Purity Standards, USA) of 0.5 and 10 mg/L of each element. The calculations of the trace element content in the probe were carried out using software of a spectrometer (thermospec, version 4.1). The detection limit (DL) was calculated as:

$$DL = C_i + 3 \times SD$$

where C_i is a mean value of the isotope content for measurements in control samples, and SD is a standard deviation of C_i determination in control samples. For elements with several isotopes, the DL corresponded to that of the most abundant isotope. The relative standard deviation (RSD) did not exceed 0.05 for elements with $C_i > 5$ DL and did not exceed 0.20 for elements with $C_i < 5$ DL. Information detailing with the NAA-SLR and ICP-AES methods used and other details of the analysis was presented in our previous publication [12,13,16,18,21].

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 INCTSBF-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, Warszawa, Poland) were analysed 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 [13,18,21].

A dedicated computer program for INAA mode optimization was used [61]. Using Microsoft Office Excel software, a summary of the statistics, including arithmetic mean, standard deviation, standard error of mean, minimum and maximum values, median, and percentiles with 0.025 and 0.975 levels was calculated for chemical element mass fractions. For elements investigated by two methods the mean of all results was used. The reliability of difference in the results between two groups was evaluated by the parametric Student's t-test. For the estimation of the Pearson correlation coefficient between different chemical elements the Microsoft Office Excel software were also used.

Results

Table 1 presents certain statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, percentiles with 0.025 and 0.975 levels) of the Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn contents in normal prostate tissue and adenocarcinoma of prostate.

The ratios of means and the reliability of difference between mean values of Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn contents in normal and cancerous prostate tissue are presented in Table 2.

Tables 3 and 4 depict results of inter-element correlation calculations (values of r–coefficient of correlation) including all pair of chemical elements identified in normal prostate tissue and adenocarcinoma of prostate, respectively.

The comparison of our results with published data for Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn contents in normal [13,16,25-42] and cancerous [34,36,38,43-53] prostate tissue is shown in Table 5.

Discussion

The INAA-SLR allowed determine the mean mass fractions of 6 chemical elements (Br, Ca, K, Mg, Mn and Na) in the tissue samples of normal and cancerous prostate glands. The ICP-AES allowed assess the mean mass fractions of 16 chemical elements (Al, B, Ba, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn) in the tissue samples of normal and cancerous prostate glands. The mass fraction of these elements were measured in all, or a major portion of normal and cancerous prostate samples. Generally, the mass fractions of V in prostate tissue samples were lower than the corresponding detection limit of ICP-AES (0.2 mg/kg, on dry-mass basis).

The use in consecutive order two analytical methods allowed us to estimate the mass fractions of 18 chemical elements in human prostate tissue. Good agreement was found between the mean values of the Ca, K, Mg, Mn, and Na mass fractions determined by non-destructive NAA-SLR and destructive ICP-AES indicating complete digestion of the prostate tissue samples (for ICP-AES 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 suggests an acceptable accuracy of the measurements performed on in prostate tissue samples.

From Tables 1 and 2, it is observed that in adenocarcinoma the mass fractions of Al, B, Ba, Br, Cu, Fe, Li, Mn, Si and Sr are significantly higher while the mass fractions of Ca, K, Mg, Na, S and Zn are significantly lower than in normal tissues of the prostate. Thus, the mass fractions of all chemical elements investigated in the study with the exception of P show significant variations in cancerous tissues when compared with normal tissues of the prostate. For example, in adenocarcinoma the mean of Al, B, Ba, Li and Mn mass fraction was almost 10, 16, 19, 7 and 5 times, respectively, greater than in normal prostate tissue (Table 2). In contrary, the Ca, Mg and Zn mass fractions were nearly 4, 3 and 8 times, respectively, and the K, Na and S mass fractions were approximately 20-40%, lower in adenocarcinoma than in normal prostate tissue (Table 2).

In normal prostate glands a statistically significant direct correlation was found, for example, between the prostatic Zn and Cu (r = 0.42), Zn and Mg (r = 0.54) and Zn and P (r = 0.85), between the prostatic Mg and Na (r = 0.53), Mg and P (r = 0.71), Mg and S (r = 0.54) and Mg and Zn (r = 0.54), between the prostatic Ca and Br (r = 0.57), and also Ca and Sr (r = 0.70), between the prostatic K and S (r = 0.68), between the prostatic Na and S (r = 0.49), between the prostatic Si and Al (r = 0.68), and between the prostatic Sr and Br (r = 0.70) (Table 3). In the same group a pronounced inverse correlation was observed between the prostatic K and Br (r = -0.46). If some positive correlations between the elements were predictable (e.g. Ca–Sr), the interpretation of other observed interrelationships requires further study for a more complete understanding.

In cancerous prostates many significant correlations between chemical elements found in the control group are no longer evident, for example, correlations for pairs with Zn, Mg, Ca, correlation between K and S, etc. (Table 4). Thus, if we accept the levels and interrelationships of chemical 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 interrelationships of chemical elements in prostate significantly changed. No published data referring to correlations

Tissue	Element	Mean	SD	SEM	Min	Max	Median	Per.	
								0.025	0.975
Normal n = 37	Al	34.1	17.7	3.5	9.6	73.3	28.9	11.9	70.8
	B	1.04	0.86	0.18	0.3	3	0.7	0.3	2.89
	Ba	1.53	1	0.21	0.38	4.33	1.18	0.42	3.75
	Br	32.9	17.7	3.6	12.5	80.7	28.2	12.6	70.9
	Ca	2428	1232	233	1180	6893	2195	1197	5553
	Cu	9.85	4.65	0.97	4.1	22.2	8.3	4.98	19.8
	Fe	132	40	7	62	218	133	67.6	212
	K	11650	2340	434	6325	18198	11403	7352	15489
	Li	0.0419	0.0264	0.0055	0.015	0.101	0.03	0.0161	0.1
	Mg	1071	409	76	447	2060	1017	520	1955
	Mn	1.32	0.42	0.09	0.75	2.8	1.3	0.836	2.23
	Na	10987	2158	393	6415	15300	10911	6718	15151
	P	7617	1839	368	5969	14838	7225	6017	11741
	S	8657	1271	254	5662	12567	8569	6680	11366
	Si	101	55	11	32.3	235	94.1	37	205
	Sr	2.34	1.86	0.38	0.87	8.1	1.47	0.916	6.43
	Zn	1061	933	153	223	5868	983	251	2342
	Al	353	255	96	43.5	765	331	46.1	730

Carcinoma n = 36	B	16.4	13.6	5.6	8	43.2	10.8	8.03	40
	Ba	29.5	26.8	10.1	1.83	72.3	22.5	2.5	70.6
	Br	95.5	37.5	10.8	16	148	102	24	143
	Ca	676	168	63	496	868	751	497	864
	Cu	18.8	10.5	3.2	4.5	30.6	12.3	5.45	30.5
	Fe	176	106	20	35	472	144	49.2	416
	K	8992	1897	717	6047	11833	9145	6231	11574
	Li	0.293	0.204	0.077	0.04	0.55	0.3	0.0419	0.547
	Mg	355	197	80	136	598	365	137	588
	Mn	7.24	5.4	2.04	1	16.2	5.8	1.2	15.5
	Na	7784	2455	928	3913	12239	7629	4379	11651
	P	6847	1897	717	2845	8546	7009	3433	8512
	S	5230	1525	576	3394	7241	5022	3482	7239
	Si	337	109	41	172	535	342	187	508
	Sr	5.56	2.24	0.84	2.1	9.2	5.5	2.42	8.9
	Zn	127	73	12	27	311	104	33.1	308

M: Arithmetic Mean; SD: Standard Deviation; SEM: Standard Error of Mean; Min: Minimum Value; Max: Maximum Value; Per. 0.025: Percentile with 0.025 level; Per. 0.975: Percentile with 0.975 level.

Table 1: Some statistical parameters of Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn mass fractions (mg/kg, dry mass basis) in normal and cancerous prostate.

Element	Prostatic tissue			Ratio
	Normal	Adenocarcinoma	Student's (t-test)	Adenocarcinoma to Normal
	41-87 year	40-79 year	*P*	
	n = 37	n = 36		
Al	34.1 ± 3.5	353 ± 96	0.016	10.4
B	1.04 ± 0.18	16.4 ± 5.6	0.04	15.8
Ba	1.53 ± 0.21	29.5 ± 10.1	0.032	19.3
Br	32.9 ± 3.6	95.5 ± 10.8	0.000092	2.9
Ca	2428 ± 233	676 ± 63	0.000000041	0.28
Cu	9.85 ± 0.97	18.8 ± 3.2	0.02	1.91
Fe	132 ± 7	176 ± 20	0.047	1.33
K	11650 ± 434	8992 ± 717	0.009	0.77
Li	0.0419 ± 0.0055	0.293 ± 0.077	0.017	6.99
Mg	1071 ± 76	355 ± 80	0.0000086	0.33
Mn	1.32 ± 0.09	7.24 ± 2.04	0.027	5.48
Na	10987 ± 393	7784 ± 928	0.012	0.71
P	7617 ± 368	6847 ± 717	0.36 (NS)	0.9
S	8657 ± 254	5230 ± 576	0.00051	0.6
Si	101 ± 11	337 ± 41	0.00091	3.34
Sr	2.34 ± 0.38	5.56 ± 0.84	0.0075	2.38
Zn	1061 ± 153	127 ± 12	0.00000054	0.12

Table 2: Comparison of mean values (M ± SEM) of Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn mass fractions (mg/kg, dry mass basis) in normal and cancerous prostate.

M: Arithmetic Mean; SEM: Standard Error of Mean; NS: Not Significant Difference

between chemical elements mass fractions in cancerous prostate tissue were found.

When our results were compared with data of literature a number of values for chemical 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% [62] and ash–1% on wet mass basis [63] contents in nonhyperplastic prostate of adult men, and also for water - 80% in cancerous tissue of prostate [64]. The obtained values for Al, B, Ba, Br, Ca, Cu, Fe, K, Mg, Mn, Na, P, S, Si, Sr and Zn mass fractions in histologically normal prostate tissue, as shown in Table 5, agree well with median of means cited by other researches for the intact prostatic tissue or nonhyperplastic prostate glands of adult males, including samples received from persons who died from various diseases. No published data referring to Li mass fractions in normal prostate tissue were found. For the adenocarcinoma of prostate the means for B, Br and Na are significantly higher than then maximum mean value of previously reported data. The means of this work for Mg, Mn and S are somewhat lower, than previously reported minimal results. No published data referring to Al, Ba, Li, Si and Sr mass fractions in cancerous tissue of prostate were found.

Characteristically, elevated or deficient levels of chemical 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 some chemical elements in adenocarcinoma could be the consequence of malignant transformation. For instance, compared to other soft tissues, the human prostate has higher levels of Ca, K, Mg, S, Zn and some other chemical elements [16-19,24]. In our previous studies we demonstrated also that the glandular lumen

Element	B	Ba	Br	Ca	Cu	Fe	K	Li
Al	-0.313	0.294	-0.002	-0.277	-0.226	0.11	0.233	0.431[a]
B	**1**	0.221	-0.253	-0.16	0.069	-0.058	0.02	0.114
Ba	0.294	**1**	0.03	-0.037	0.078	-0.193	-0.058	0.553[b]
Br	-0.002	0.03	**1**	0.572[b]	0.266	-0.012	-0.458[a]	0.156
Ca	-0.277	-0.037	0.572[b]	**1**	0.222	0.056	-0.224	-0.092
Cu	-0.226	0.078	0.266	0.222	**1**	0.229	-0.096	-0.074
Fe	0.11	-0.193	-0.012	0.056	0.229	**1**	0.03	-0.025
K	0.233	-0.058	-0.458[a]	-0.224	-0.096	0.03	**1**	-0.198
Li	0.431[a]	0.553[b]	0.156	-0.092	-0.074	-0.025	-0.198	**1**
Mg	0.027	0.199	-0.062	-0.034	0.411	-0.042	0.203	-0.027
Mn	0.083	0.1	-0.121	-0.223	0.398	0.363	0.099	0.106
Na	-0.38	0.077	-0.251	-0.118	0.148	0.204	0.226	0.085
P	-0.025	0.235	-0.085	0.189	0.366	0.05	0.211	-0.143
S	-0.072	0.307	-0.319	-0.281	0.122	0.227	0.676[c]	0.011
Si	-0.033	0.242	-0.378	-0.289	-0.253	-0.081	0.325	0.423[a]
Sr	-0.157	0.269	0.699[c]	0.604[b]	-0.028	-0.237	-0.408	0.469[a]
Zn	-0.145	0.162	0.057	0.042	0.424[a]	0.008	-0.016	-0.154
Element	Mg	Mn	Na	P	S	Si	Sr	Zn
Al	-0.152	0.22	0.061	0.233	0.288	0.679[c]	0.029	-0.133
B	0.027	0.083	-0.38	-0.025	-0.072	-0.033	-0.157	-0.145
Ba	0.199	0.1	0.077	0.235	0.307	0.242	0.269	0.162
Br	-0.062	-0.121	-0.251	-0.085	-0.319	-0.378	0.699[c]	0.057
Ca	-0.034	-0.223	-0.118	0.189	-0.281	-0.289	0.604[b]	-0.042
Cu	0.411	0.398	0.148	0.366	0.122	-0.253	-0.028	0.424[a]
Fe	-0.042	0.363	0.204	0.05	0.227	-0.081	-0.237	0.008
K	0.203	0.099	0.226	0.211	0.676[c]	0.325	-0.408	-0.016
Li	-0.027	0.106	0.085	-0.143	0.011	0.423[a]	0.469[a]	-0.154
Mg	**1**	0.142	0.523[b]	0.706[c]	0.539[b]	-0.096	-0.208	0.535[b]
Mn	0.142	**1**	0.087	-0.041	0.22	0.165	-0.168	-0.045
Na	0.523[b]	0.087	**1**	0.148	0.494[a]	0.201	-0.178	0.212
P	0.706[c]	-0.041	0.148	**1**	0.344	-0.125	-0.245	0.845[c]
S	0.539[b]	0.22	0.494[a]	0.344	**1**	0.241	-0.302	0.08
Si	-0.096	0.165	0.201	-0.125	0.241	**1**	0.146	-0.201
Sr	-0.208	-0.168	-0.178	-0.245	-0.302	0.146	**1**	-0.278
Zn	0.535[b]	-0.045	0.212	0.845[c]	0.08	-0.201	-0.278	**1**

Table 3: Intercorrelations (r: coefficient of correlation) of pairs of the Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr, and Zn mass fractions in normal prostate glands.

and, therefore, the prostatic fluid is the main pool of Ca, K, Mg, S, Zn accumulation in the normal human prostate [14,65-68]. These data suggests that these elements could be involved in functional features of prostate tissue. Moreover, it is plausible that the reason for the emergence and development of adenocarcinoma is associated with abnormally high concentration of Zn, Ca and Mg in the prostate tissue of older men [10,11,14,23]. However, malignant transformation is accompanied by a loss of tissue-specific functional features, including the prostatic fluid production, which leads to a significant reduction in the contents of such chemical elements as Ca, K, Mg, S, and Zn associated with functional characteristics of the human prostate tissue.

On the other hand, the well documented fact that the cancer cells, including adenocarcinoma of human prostate, are under high levels of oxidative stress [69]. The cancer cells exposed to oxidative stress tend to forced adaptation mechanisms including production higher levels of antioxidant enzymes such as manganese-containing superoxide dismutase (Mn-SOD). Mn-SOD has been shown to be high in human tumors including lung cancer [70], ovarian carcinoma [71,72], thyroid tumours [73], renal cell carcinoma [74], brain tumors [75], esophageal and gastric cancers [76,77], malignant mesothelioma [78,79], hepatocellular carcinoma [80], colorectal tumors [81], breast cancer [82] and some other tumors [83] as compared to corresponding non-malignant control tissues. It was reported also that intracellular Mn content was positively correlated with Mn-SOD, suggesting that the intracellular Mn level is associated with Mn-SOD activity [79]. In cited study was shown that the human mesothelioma cells contained an extremely high level of Mn, an amount 7.3-fold higher than that in the human mesothelial cells [79]. Such great difference between Mn content in normal and malignant cells agrees well with our result for normal and cancerous prostate tissue (Table 2).

Some environmental factors linked to pca pathogenesis include diet, specifically red meat, which is one of the main sources of Fe supply. Iron is very important in many physiological processes but it is toxic when it is present in excess. The carcinogenic potential of Fe in pca is not fully understood however one of the possible way is a link between iron-induced oxidative stress and inflammation [84,85]. Otherwise, it is well known that Fe mass fraction in sample depends mainly from the blood volumes in tissues. Cancerous tissues are predominantly hyper vascular lesions [86-89]. Thus, it is possible to speculate that prostate adenocarcinoma is characterized by an increase of the mean value of

Element	B	Ba	Br	Ca	Cu	Fe	K	Li
Al	0.696	0.825[a]	0.364	0.029	0.481	-0.415	0.109	0.910[b]
B	**1**	0.555	0.319	0.127	0.524	-0.205	0.492	0.729
Ba	0.555	**1**	0.335	0.013	0.088	-0.158	-0.177	0.596
Br	0.319	0.335	**1**	-0.255	0.107	-0.171	0.461	0.337
Ca	0.127	0.013	-0.255	**1**	0.046	0.415	0.314	0.061
Cu	0.524	0.088	0.107	0.046	**1**	-0.145	0.587	0.755[a]
Fe	-0.205	-0.158	-0.171	0.415	-0.145	**1**	-0.336	-0.386
K	0.492	-0.177	0.461	0.314	0.587	-0.336	**1**	0.296
Li	0.729	0.596	0.337	0.061	0.755[a]	-0.386	0.296	**1**
Mg	0.304	0.129	-0.082	0.405	0.187	-0.182	0.357	-0.022
Mn	0.081	0.405	0.213	0.003	0.365	-0.245	0.001	0.69
Na	0.192	-0.248	0.378	0.251	0.353	-0.399	0.916[b]	0.011
P	0.362	0.458	0.567	-0.107	0.465	-0.771[a]	0.558	0.515
S	0.446	0.068	0.079	0.199	0.104	-0.509	0.568	-0.036
Si	0.434	0.387	0.658	0.044	0.587	-0.16	0.404	0.816[a]
Sr	0.482	0.425	-0.027	0.411	0.559	-0.58	0.495	0.597
Zn	-0.168	-0.168	0.109	0.596	0.082	-0.052	0.519	-0.421
Element	Mg	Mn	Na	P	S	Si	Sr	Zn
Al	0.081	0.61	-0.09	0.109	0.062	0.686	0.598	-0.448
B	0.304	0.081	0.192	0.362	0.446	0.434	0.482	-0.168
Ba	0.129	0.405	-0.248	0.458	0.068	0.387	0.425	-0.378
Br	-0.082	0.213	0.378	0.567	0.079	0.658	-0.027	0.109
Ca	0.405	0.003	0.251	-0.107	0.199	0.044	0.411	0.596
Cu	0.187	0.365	0.353	0.465	0.104	0.587	0.559	0.082
Fe	-0.182	-0.245	-0.399	-0.771[a]	-0.509	-0.16	-0.58	-0.052
K	0.357	0.001	0.916[b]	0.558	0.568	0.404	0.495	0.519
Li	-0.022	0.69	0.011	0.515	-0.036	0.816[a]	0.597	-0.421
Mg	**1**	-0.498	0.437	0.411	0.717	-0.199	0.455	0.651
Mn	-0.498	**1**	-0.143	0.346	-0.357	0.728	0.355	-0.474
Na	0.437	0.143	**1**	0.594	0.711	0.129	0.472	0.706
P	0.411	0.346	0.594	**1**	0.592	0.469	0.684	0.128
S	0.717	-0.357	0.711	0.592	**1**	-0.193	0.589	0.656
Si	-0.199	0.728	0.129	0.469	-0.193	**1**	0.26	-0.419
Sr	0.455	0.355	0.472	0.684	0.589	0.26	**1**	0.347
Zn	0.651	-0.474	0.706	0.128	0.656	-0.419	0.347	**1**

Statistically significant difference: [a]$p \le 0.05$; [b]$p \le 0.01$; [c]$p \le 0.001$

Table 4: Intercorrelations (r: coefficient of correlation) of pairs of the Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr, and Zn mass fractions in cancerous prostate glands.

the Fe mass fraction because the level of tumor vascularization is higher than that in normal prostate tissue.

Numerous studies in the literature have reported that tumour Cu levels are elevated in a variety of malignancies [90]. This phenomena may be bound with a role of Cu ions in oxidative stress [90,91] and also with tumor angiogenesis because Cu ions stimulate blood vessel development [92].

Bromide compounds, especially potassium bromide (kbr), sodium bromide (nabr), and ammonium bromide (NH_4Br), are frequently used as sedatives in Russia [93]. It may be the reason for elevated level of Br in tissue specimens of patients with adenocarcinoma of prostate gland.

Reasons of the elevated levels of Al, B, Ba, Li, Si and Sr in prostate adenocarcinoma in comparison with non-cancerous gland are unclear and need special investigations.

To clarify the role of chemical elements in prostate tumorogenesis, the mass fractions of Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, S, Si, Sr and Zn and the interrelationships of these chemical element mass fractions were investigated only in the adenocarcinoma of prostate gland. In future studies of the role of chemical elements in tumorogenesis of the prostate gland the specimens of prostate cancer with other histopathologic feature have to be included. Moreover, there are many other chemical elements involved in normal metabolism and pathophysiology of the prostate gland. Thus, further studies are needed to extend the list of chemical elements investigated in this manner.

Conclusion

The combination of nondestructive INAA-SLR and destructive ICP-AES methods is satisfactory Analytical tool for the precise determination of 17 chemical element mass fractions in the tissue. Samples of prostate adenocarcinoma and normal prostate glands. The sequential application of two Methods allowed precise quantitative determinations of mean mass fraction of Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn. It was observed that the mass fractions of all Chemical elements investigated in the study with the exception of P show significant variations in Cancerous tissues when compared with normal tissues of the prostate. Moreover, it was shown that

Prostate tissue	Element	Published data [Reference]			This work
		Median of means	Minimum of means	Maximum of means	
		(n)[a]	M or M ± SD, (n)[b]	M or M ± SD, (n)[b]	M ± SD
Normal	Al	34.2 (6)	13 ± 66 (50) [25]	59 (9) [26]	34.1 ± 17.7
	B	1.0 (10)	<0.47 (50) [25]	1.2 (1) [27]	1.04 ± 0.86
	Ba	1.75 (10)	0.12 (50) [25]	102 ± 82 (10) [28]	1.53 ± 1.00
	Br	30.0 (18)	14 ± 9 (4) [29]	50 ± 32 (10) [30]	32.9 ± 17.7
	Ca	1990 (22)	427 ± 117 (21) [31]	7500 ± 12300 (57) [32]	2428 ± 1232
	Cu	9.6 (28)	1.37 (-) [33]	1488 ± 47 (10) [34]	9.85 ± 4.65
	Fe	118 (34)	5.7 ± 0.1 (5) [35]	1224 ± 76 (10) [34]	132 ± 40
	K	11800 (20)	4360 ± 364 (27) [36]	13000 ± 660 (16) [16]	11650 ± 2340
	Li	-	-	-	0.042 ± 0.026
	Mg	1020 (21)	498 ± 172 (13) [32]	2056 ± 476 (21) [31]	1071 ± 409
	Mn	1.48 (24)	<0.47 (12) [37]	106 ± 18 (5) [38]	1.32 ± 0.42
	Na	10500 (16)	23 ± 26 (13[32]	13700 ± 3500 (4) [39]	10987 ± 2158
	P	7120 (15)	2060 ± 690 (13) [32]	14500 (12) [37]	7617 ± 1839
	S	7370 (6)	5300 ± 750 (57) [32]	8810 ± 730 (16) [18]	8657 ± 1271
	Si	100 (6)	51 (1) [40]	111 ± 64 (64) [13]	101 ± 55
	Sr	1.46 (13)	0.75 ± 0.09 (48) [25]	2.61 ± 3.07 (27) [41]	2.34 ± 1.86
	Zn	525 (75)	101 (1) [42]	3218 ± 41 (10) [34]	1061 ± 933
Adeno- cacinoma	Al	-	-	-	353 ± 255
	B	1.78 (1)	1.78 ± 0.65 (23) [43]	1.78 ± 0.65 (23) [43]	16.4 ± 13.6
	Ba	-	-	-	29.5 ± 26.8
	Br	1.5 (1)	1.5 ± 0.6 (27) [36]	1.5 ± 0.6 (27) [36]	95.5 ± 37.5
	Ca	1830 (10)	658 ± 109 (12) [44]	11200 (1) [45]	676 ± 168
	Cu	13 (14)	4.0 ± 3.0 (11) [46]	1930 ± 65 (10) [34]	18.8 ± 10.5
	Fe	195 (15)	12.5 ± 5.0 (20) [47]	6850 (1) [45]	176 ± 106
	K	5600 (5)	740 ± 90 (27) [36]	18100 ± 400 (4) [48]	8992 ± 1897
	Li	-	-	-	0.293 ± 0.204
	Mg	935 (5)	361 ± 174 (25) [49]	1050 ± 720 (11) [46]	355 ± 197
	Mn	17.3 (6)	8.0 ± 2.0 (3) [50]	160 ± 22 (5) [38]	7.24 ± 5.40
	Na	5100 (1)	5100 (4) [51]	5100 (4) [51]	7784 ± 2455
	P	5400 (3)	3620 ± 680 (12) [44]	7700 ± 3900 (12) [52]	6847 ± 1897
	S	6900 (1)	6900 ± 1100 (12)[44]	6900 ± 1100 (12) [44]	5230 ± 1525
	Si	-	-	-	337 ± 109
	Sr	-	-	-	5.56 ± 2.24
	Zn	200 (44)	16.7 ± 3.5 (3) [50]	840 ± 85 (13) [53]	127 ± 73

Table 5: Median, minimum and maximum value of means of Al, B, Ba, Br, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr and Zn mass fractions (mg/kg, dry mass basis) in normal and cancerous prostate according to data from the literature in comparison with our results.
M: Arithmetic Mean; SD: Standard Deviation; (n)[a]: Number of All References; (n)[b]: Number of Samples.

Malignant transformation significantly changed the interrelationships 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.

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