OPEN ACCESS
Freely Available Online

JOURNAL OF HEMATOLOGY AND ONCOLOGY RESEARCH
ISSN NO: 2372-6601

RESEARCH ARTICLE
DOI : 10.14302/issn.2372-6601.jhor-15-896

The Bromine, Calcium, Potassium, Magnesium, Manganese, and Sodium Contents in Adenocarcinoma of Human Prostate Gland

Vladimir Zaichick [1*], Sofia Zaichick [2]

1. Radionuclide Diagnostics Department, Medical Radiological Research Centre, Obninsk 249036, Russia.
2. Department of Medicine, University of Illinois, College of Medicine at Chicago, Chicago, IL 60612, USA

Abstract

Objectives: Adenocarcinoma of prostate 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 calcium (Ca), potassium (K), and magnesium (Mg) as an androgen dependent chemical element, and bromine (Br), manganese (Mn), and sodium (Na), as androgen independent elements, exist in the malignantly transformed prostate.

Methodology: Prostatic tissue levels of Br, Ca, K, Mg, Mn, and Na contents were prospectively evaluated in 10 patients with adenocarcinoma and 37 healthy male inhabitants. Measurements were performed using non-destructive instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides. 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.

Key results: Mean values ± standard error of means (M±SEM) for mass fraction (mg/kg on dry mass basis) of chemical element in the normal tissue were: Br 32.9±3.6, Ca 2280±178, K 11211±414, Mg 1118±76, Mn 1.24±0.07, and Na 11100±408, respectively. The contents of Br and Mn were significantly higher (approximately 4 and 6 times, respectively) while those of Ca and Mg (nearly 3 times) and K and Na (20% and 30%, respectively) were significantly lower in cancerous tissues than in normal tissues.

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

Corresponding author:

Prof. Dr. Vladimir Zaichick, Medical Radiological Research Centre, Koroleva St. 4, Obninsk 249036, Kaluga Region, Russia, Fax: +7 495 956 1440, Phone: +7 48439 60289, E-mail: vezai@obninsk.com

Citation: Vladimir Zaichick, Sofia Zaichick (2016) The Bromine, Calcium, Potassium, Magnesium, Manganese, and Sodium Contents in Adenocarcinoma of Human Prostate Gland. Journal of Hematology and Oncology Research - 2(2):1-12. https://doi.org/10.14302/issn.2372-6601.jhor-15-896

Editor: Krzysztof Roszkowski, Nicolaus Copernicus University, PL. Department of Oncology, Radiotherapy and Gynecologic Oncology

Keywords: Chemical elements; human prostate gland; adenocarcinoma; neutron activation analysis

Running title: Chemical elements in prostatic adenocarcinoma

Received Dec 16, 2015; **Accepted** Feb 02, 2016; **Published** Feb 06, 2016

Introduction

Prostate cancer (PCa) is the most common non-cutaneous male cancer in most populations.[1] Although the etiology of PCa is unknown, several risk factors including diet (calcium and some other nutrients) have been well identified.[2,3] 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.[3,4]

Chemical 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 chemical elements depend on tissue-specific need or tolerance, respectively.[5] Excessive accumulation or an imbalance of the chemical elements may disturb the cell functions and may result in cellular degeneration or death.[5-7]

High intraprostatic calcium (Ca) concentrations are probably one of the main factors acting in both initiation and promotion stages of prostate carcinogenesis.[8-10] A significant tendency of age-related increase in Ca, magnesium (Mg), zinc, and many other chemical element mass fraction in the normal prostate was recently demonstrated by us. [9-19] Moreover, it was found that the prostatic tissue content of Ca, potassium (K), and Mg are an androgen dependent chemical element, but content of bromine (Br), manganese (Mn), and sodium (Na) are not bound to levels of sex hormone.[20] Thus, it seems fair to suppose that besides Ca, many other chemical elements also play a role in the pathophysiology of the prostate.

The chemical element contents in tissue of the normal[21-28] and cancerous[29-34] 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 ashed before analysis. In other cases, prostate samples are treated with solvents (distilled water, ethanol etc) and then are dried at a high temperature for many hours. There is evidence that certain quantities of chemical elements are lost as a result of such treatment.[35-37] Moreover, 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.

This work had two aims. The first aim was to obtain reliable values for the Br, Ca, K, Mg, Mn, and Na contents in the prostate cancer and in the normal prostate gland using non-destructive instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR). The second aim was to compare the levels of chemical elements in normal and cancerous tissue.

Material and Methods

All patients suffered from adenocarcinoma of prostate (n=10, mean age M±SD was 65±10 years, range 51-77) 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. All samples of cancerous tissue were obtained before hormonal or radiation therapy.

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.

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 labeled polyethylene ampoules.

To determine the contents of the chemical elements by comparison with known data for standard, aliquots of commercial, chemically pure compounds, synthetic and natural reference materials were used.[38] Ten sub-samples of international certified reference material (CRM) IAEA H-4 (animal muscle) weighing about 100 mg were treated and analyzed under exactly the same conditions as the prostate samples, to allow estimation of the precision and accuracy of results.

The content of Br, Ca, K, Mg, Mn, and Na were determined by INAA-SLR using a horizontal channel equipped with the pneumatic rabbit system of the WWR-c research nuclear reactor. The neutron flux in the channel was 1.7×10^{13}n cm^{-2} s^{-1}. Ampoules with prostate samples, biological synthetic standards, intralaboratory-made standards, and certified reference material were put into polyethylene rabbits and then irradiated separately for 180 s. Copper foils were used to assess neutron flux.

The measurement of each sample was made twice, 1 min and 120 min after irradiation. The duration of the first and second measurements was 10 min and 20 min, respectively. A coaxial 98-cm3 Ge (Li) detector and a spectrometric unit (NUC 8100), including a PC-coupled multichannel analyzer, were used for measurements. The spectrometric unit provided 2.9-keV resolution at the ^{60}Co 1,332-keV line. Details of used nuclear reactions, radionuclides, and gamma-energies were presented in our earlier publication concerning the INAA-SLR chemical element contents in human scalp hair.[39]

All prostate samples for INAA-SLR were prepared in duplicate and mean values of chemical element contents were used in final calculation. Using the Microsoft Office Excel software, the summary of statistics, arithmetic mean, standard deviation, standard error of mean, minimum and maximum values, median, percentiles with 0.025 and 0.975 levels were calculated for chemical element contents in normal and cancerous prostate tissues. The reliability of difference in the results between the two groups of prostate tissue samples was evaluated by Student's *t*-test. For the estimation of the Pearson correlation coefficient between different pairs of the chemical element mass fractions in

the normal and cancerous prostate tissues the Microsoft Office Excel software was also used.

Results

Table 1 depicts our data for Br, Ca, K, Mg, Mn, and Na mass fractions in ten sub-samples of CRM IAEA H-4 (animal muscle) certified reference material and the certified values of this material.

Table 2 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 Br, Ca, K, Mg, Mn, and Na contents in normal prostate tissue and adenocarcinoma of prostate.

The ratios of means and the reliability of difference between mean values of Br, Ca, K, Mg, Mn, and Na contents in normal and cancerous prostate tissue are presented in Table 3.

Table 4 depicts results of inter-element correlation calculations (values of *r* – coefficient of correlation) including all pair of chemical elements

Table 1. NAA-SLR data Br, Ca, K, Mg, Mn, and Na mass fractions (mg/kg, dry mass basis) in the IAEA H-4 (animal muscle) reference material compared to certified values

Element	Certified values			This work results
	Mean	95% confidence interval	Type	Mean±SD
Br	4.1	3.5 - 4.7	C	5.0±0.9
Ca	188	163 - 213	C	238±59
K	15800	15300 - 16400	C	16200±380
Mg	1050	990 - 1110	C	1100±190
Mn	0.52	0.48 – 0.55	N	0.55±0.11
Na	2060	1930 - 2180	C	2190±140

Mean – arithmetical mean, SD – standard deviation, C- certified values, N – non-certified values.

Table 2. Some statistical parameters of Br, Ca, K, Mg, Mn, and Na mass fractions (mg/kg, dry mass basis) in normal and cancerous prostate

Tissue	Element	Mean	SD	SEM	Min	Max	Median	Per. 0.025	Per. 0.975
Normal	Br	32.9	17.7	3.6	12.5	80.7	28.2	12.6	70.9
n=37	Ca	2280	874	178	1205	4908	2082	1340	4386
	K	11211	2071	414	7100	14328	11399	7100	13998
	Mg	1118	396	76	604	2060	1062	626	1963
	Mn	1.24	0.32	0.07	0.40	1.80	1.30	0.65	1.75
	Na	11100	2159	408	6834	15300	11071	6879	15161
Adeno-	Br	120	29	9	69.3	169	116	75.1	165
carcinoma	Ca	676	168	63	496	868	751	497	864
n=10	K	8991	1897	717	6047	11833	9145	6231	11574
	Mg	354	197	80	136	598	365	137	588
	Mn	7.2	5.4	2.0	1.00	16.2	5.80	1.20	15.5
	Na	7784	2455	928	3913	12239	7629	4379	11651

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 3. Comparison of mean values (M±SEM) of Br, Ca, K, Mg, Mn, and Na mass fractions (mg/kg, dry mass basis) in normal and cancerous prostate

Element	Prostatic tissue			Ratio
	Normal 41-87 year n=37	Adenocarcinoma 51-77 year n=10	Student's (*t*-test) *p*£	Adenocarcinoma to Normal
Br	32.9±3.6	120±9	0.0000016	3.65
Ca	2280±178	676±63	0.0000000038	0.30
K	11211±414	8991±717	0.022	0.80
Mg	1118±76	354±80	0.0000042	0.32
Mn	1.24±0.07	7.2±2.0	0.026	5.81
Na	11100±408	7784±928	0.010	0.70

M - arithmetic mean, SEM – standard error of mean, NS - not significant difference

Table 4. Intercorrelations (*r* – coefficient of correlation) of pairs of the trace element mass fractions in normal and cancerous prostate glands

Tissue	Element	Br	Ca	K	Mg	Mn	Na
Normal	Br	**1.00**	0.248	-0.342[a]	0.169	-0.105	-0.074
	Ca	0.248	**1.00**	0.263[a]	0.216	-0.367[b]	-0.127
	K	-0.342[a]	0.263[a]	**1.00**	-0.364[b]	-0.171	-0.126
	Mg	0.169	0.216	-0.364[b]	**1.00**	-0.064	0.417[b]
	Mn	-0.105	-0.367[b]	-0.171	-0.064	**1.00**	0.392[b]
	Na	-0.074	-0.127	-0.126	0.417[b]	0.392[b]	**1.00**
Adenocarcinoma	Br	**1.00**	-0.657	0.539	0.303	-0.143	0.562
	Ca	-0.657	**1.00**	0.197	-0.107	-0.073	0.076
	K	0.539	0.197	**1.00**	0.225	-0.002	0.943[c]
	Mg	0.303	-0.107	0.225	**1.00**	-0.622	0.267
	Mn	-0.143	-0.073	-0.002	-0.622	**1.00**	-0.079
	Na	0.562	0.076	0.943[c]	0.267	-0.079	**1.00**

identified in normal prostate tissue and adenocarcinoma of prostate.

The comparison of our results with published data for Br, Ca, K, Mg, Mn, and Na contents in normal and cancerous prostate tissue is shown in Table 5.

From Tables 2 and 3, it is observed that in adenocarcinoma the mass fractions of Br (p<0.0000016) and Mn (p<0.026) are significantly higher while the mass fractions of Ca (p<0.0000000038), K (p<0.022), Mg (p<0.0000042), and Na (p<0.010) are significantly lower than in normal tissues of the prostate. Thus, the

Table 5. Median, minimum and maximum value of means of Br, Ca, K, Mg, Mn, and Na mass fractions (mg/kg, dry mass basis) in normal and cancerous prostate according to data from the literature in comparison with our results

Prostate tissue	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
Normal	Br	14.5 (2)	12±8 (4)[21]	17 (12)[22]	33±18
	Ca	1500(11)	430±120 (21)[23]	7500±12300 (57)[24]	2280±874
	K	10000(10)	6850 (1)[25]	12200±1500 (8)[26]	11211±2071
	Mg	900(12)	498±172 (13)[24]	2056±476 (21)[27]	1118±396
	Mn	1.0 (6)	<0.47 (12)[22]	7.25±5.00 (4)[28]	1.24±0.32
	Na	6100(7)	23±26 (13)[24]	11700±3000 (4)[28]	11100±2159
Adeno-carcinoma	Br	1.5 (1)	1.5±6.0 (27)[29]	1.5±6.0 (27)[29]	120±29
	Ca	2940 (7)	1100 (4)[30]	410000±43000 (1)[31]	676±168
	K	3620 (4)	740±90 (27)[29]	5600 (4)[30]	8991±1897
	Mg	935 (5)	361±174 (25)[32]	1050±720 (11)[33]	354±197
	Mn	8.0 (4)	2.74±0.27 (1)[31]	160±22 (1)[34]	7.2±5.4
	Na	5100 (1)	5100 (4)[30]	5100 (4)[30]	7784±2455

M - arithmetic mean, SD – standard deviation, (n)[a] – number of all references, (n)[b] - number of samples.

Discussion

As was shown by us the use of CRM IAEA H-4 as a certified reference material for the analysis of chemical elements contents in samples of prostate tissue can be seen as quite acceptable.[9] Good agreement of the Br, Ca, K, Mg, Mn, and Na mass fractions analyzed by INAA-SLR with the certified data of CRM IAEA (Table 1) indicates an acceptable accuracy of the results obtained in the study of chemical elements of the human prostatic adenocarcinoma presented in Tables 2–5.

The mean values and all selected statistical parameters were calculated for 6 chemical elements (Br, Ca, K, Mg, Mn, and Na) (Table 2). The mass fraction of these elements were measured in all, or a major portion of normal and cancerous prostate samples.

mass fractions of all chemical elements investigated in the study show significant variations in cancerous tissues when compared with normal tissues of the prostate. For example, in adenocarcinoma the mean of Mn mass fraction was almost 6 times, and the mean of Br mass fraction was approximately 4 times, greater than in normal prostate tissue (Table 3). In contrary, the Ca and Mg mass fractions were nearly 3 times, and the K and Na mass fractions were approximately 20-30%, lower in adenocarcinoma than in normal prostate tissue (Table 3).

In healthy prostate tissue a half proportion (3 out of 6) of statistically significant inter-element correlations were observed for K: positive correlation

with Ca (p<0.05) and inverse correlations with Br (p<0.05), and Mg (p<0.01) (Table 4). The positive inter-element correlations of Mn mass fractions with Na (p<0.01) and inverse correlations with Ca (p<0.01) mass fractions were also found in healthy prostate tissue. Additionally, levels of Mg have significant relationships with Na (p<0.01. These correlations indicate a possible connection between these elements and the normal function of the prostate. Inter-element correlations between chemical elements contents differ markedly in adenocarcinoma of prostate as compared to their relationships in normal prostate tissue. Only K contents have positive correlation with Na (p<0.001). Published data referring to inter-element correlations of Br, Ca, K, Mg, Mn, and Na mass fractions in normal and cancerous tissues of the human prostate gland were not found.

The results for all chemical element contents in the prostates of the control group (mean age 55±11 years, range 41-87) are in accordance with our earlier findings in prostates of apparently healthy men aged 41-60.[9] In data from the literature a number of values for chemical element mass fractions in prostate tissue were not expressed on a dry mass basis. Therefore, we calculated these values using published data for water - 80% and ash - 1% on wet mass basis contents in the prostate of adult men.[40,41] This reported data also includes samples obtained from patients who died from different non-urological diseases. Values obtained for Br, Ca, K, Mg, Mn, and Na contents agree well with median of mean values cited by other researches for the human prostate (Table 5). In the adenocarcinoma of prostate our results were only comparable with published data for Mn and Na contents. Mean mass fractions of Ca and Mg found in this study were approximately 3-4 times lower than the means of reported data, while mean value of Br almost two orders of magnitude higher (Table 5).

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 chemical elements in adenocarcinoma could be the consequence of malignant transformation. Compared to other soft tissues, the human prostate has higher levels of Ca, K, Mg, and some other chemical elements.[12,42] 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 Ca and Mg in the prostate tissue of older men. Malignant transformation is accompanied by a loss of tissue-specific functional features, which leads to a significant reduction in the contents of such chemical elements as Ca, K, and Mg 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.[43] 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[44], ovarian carcinoma[45,46], thyroid tumours[47], renal cell carcinoma[48], brain tumors[49], esophageal and gastric cancers[50,51], malignant mesothelioma[52,53], hepatocellular carcinoma[54], colorectal tumors[55], breast cancer[56], and some other tumors[57] 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.[58] 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.[58] Such great difference between Mn content in normal and malignant cells agrees well with our result for Mn mass fractions in normal and cancerous prostate tissue (Table 3).

Bromide compounds, especially potassium bromid (KBr), sodium bromide (NaBr), and ammonium bromide (NH_4Br), are frequently used as sedatives in Russia.[59] It may be the reason for elevated levels of Br in specimens of patients with adenocarcinoma of prostate glad.

Our findings show that mass fraction of Ca, K, Mg, and Mn are significantly different in most adenocarcinomas as compared to normal prostate tissues (Tables 3). Thus, it is plausible to assume that levels of these chemical elements in prostate tissue can be used as tumor markers. However, this subjects needs in additional studies.

Conclusion

In this work, chemical elemental analysis was carried out in the tissue samples of normal prostate and adenocarcinoma of prostate using INAA-SLR. It was shown that INAA-SLR is an adequate analytical tool for the non-destructive determination of Br, Ca, K, Mg, Mn, and Na content in the tissue samples of human prostate, including needle-biopsy cores. It was observed that in cancerous tissues contents of Ca, K, Mg, and Na were significantly lower and those of Br and Mn were significantly higher than in normal tissues. In our opinion, the abnormal decrease in levels of Ca, K, and Mg, as well as the increase in level of Mn in cancerous tissue could be a consequence of malignant transformation. It was supposed that elevated level of Mn as well as decreased levels of Ca, K, and Mg in prostatic tissue can be used as tumor markers.

Acknowledgements

The authors are grateful to Dr Tatyana Sviridova, Medical Radiological Research Center, Obninsk, and Prof. A.A. Zhavoronkov, Institute of Human Morphology, Russian Academy of Medical Sciences, Moscow, for supplying prostate samples.

Conflict of interest

Authors have declared that no competing interest exist.

Ethical approval

The study was approved by the Ethical Committee of the Medical Radiological Research Center, Obninsk.

References

1. Rebbeck, T.R. and Haas, G.P. (2014) Temporal trends and racial disparities in global prostate cancer prevalence. *Can. J. Urol. 21*, 7496-7506
2. Yamada, K., Araki, S., Tamura, M., Saka Y., Takahashi, M. et al. (2000) Epidemiologic determinants of clinically relevant prostate cancer. *Int. J. Cancer 89*, 259-26
3. Rebbeck, T.R. (2006) Conquering cancer disparities: new opportunities for cancer epidemiology,

biomarker, and prevention research. *Cancer Epidemiol. Biomarkers Prev. 15*, 1569-1571

4. Jemal, A., Murray, T., Samuels, A., Ghafoor, A., Ward, E. et al. (2003) Cancer statistics, 2003. *CA: A Cancer Journal for Clinicians 53*, 5-26
5. Zaichick, V. (2006) Medical elementology as a new scientific discipline. *J. Radioanal. Nucl. Chem. 269*, 303-309
6. Ektessabi, A., Shikine, S., Kitamura, N., Rokkum, M., and Johansson, C. (2001)Distribution and chemical states of iron and chromium released from orthopedic implants into human tissues. *X-Ray Spectrom. 30*, 44–48
7. Yoshida, S., Ektessabi, A., and Fujisawa, S. (2001) XAFS spectroscopy of a single neuron from a patient with Parkinson's disease. *J. Synchrotron Radiat. 8*, 998–1000
8. Isaacs, J.T. (1983) Prostatic structure and function in relation to the etiology of prostatic cancer. *Prostate 4(4)*, 351-366
9. Zaichick, S. and Zaichick V. (2011) INAA application in the age dynamics assessment of Br, Ca, Cl, K, Mg, Mn, and Na content in the normal human prostate. *J. Radioanal. Nucl. Chem. 288()*, 197-202
10. Zaichick, V., Nosenko, S., and Moskvina, I. (2012) The effect of age on 12 chemical element contents in intact prostate of adult men investigated by inductively coupled plasma atomic emission spectrometry. *Biol. Trace Elem. Res. 147(1-3)*, 49-58
11. Zaichick, S. and Zaichick V. (2011) The effect of age on Ag, Co, Cr, Fe, Hg, Sb, Sc, Se, and Zn contents in intact human prostate investigated by neutron activation analysis. *Appl. Radiat. Isot. 69(6)*, 827-833
12. Zaichick, V. and Zaichick, S. (2013) The effect of age on Br, Ca, Cl, K, Mg, Mn, and Na mass fraction in pediatric and young adult prostate glands investigated by neutron activation analysis. *Appl. Radiat. Isot. 82*, 145-151
13. Zaichick, V. and Zaichick, S. (2013) INAA application in the assessment of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn mass fraction in pediatric and young adult prostate glands. *J. Radioanal. Nucl. Chem. 298 (3),* 1559-1566
14. Zaichick, V. and Zaichick, S. (2013) NAA-SLR and ICP-AES Application in the assessment of mass fraction of 19 chemical elements in pediatric and young adult prostate glands. *Biol. Trace Elem. Res. 156(1)*, 357-366
15. Zaichick, V. and Zaichick, S. (2013) Use of neutron activation analysis and inductively coupled plasma mass spectrometry for the determination of trace elements in pediatric and young adult prostate. *American Journal of Analytical Chemistry 4*, 696-706
16. Zaichick, V. and Zaichick, S. (2014) INAA application in the assessment of chemical element mass fractions in adult and geriatric prostate glands. *Appl. Radiat. Isot. 90*, 62-73
17. Zaichick, V. and Zaichick, S. (2014) Determination of trace elements in adults and geriatric prostate combining neutron activation with inductively coupled plasma atomic emission spectrometr. *Open Journal of Biochemistry 1(2)*, 16-33
18. Zaichick, V. and Zaichick, S. (2014). Use of INAA and ICP-MS for the assessment of trace element mass

fractions in adult and geriatric prostate. *J. Radioanal. Nucl. Chem. 301()*, 383-397

19. Zaichick, V. (2015) The variation with age of 67 macro- and microelement contents in nonhyperplastic prostate glands of adult and elderly males investigated by nuclear analytical and related methods. *Biol. Trace Elem. Res. 168(1)*, 44-60
20. Zaichick, V. and Zaichick, S. (2014) Androgen-dependent chemical elements of prostate gland', *Andrology & Gynecology: Current Research 2(2)* doi:10.4172/2327-4360.1000121
21. Kubo, H., Hashimoto, S., Ishibashi, A., Chiba, R., and Yokota, H. (1976) Simultaneous determinations of Fe, Cu, Zn, and Br concentrations in human tissue sections. *Medical Physics 3*, 204-209
22. Forssen, A. (1972) Inorganic elements in the human body. I. Occurrence of Ba, Br, Ca, Cd, Cs, Cu, K, Mn, Ni, Sn, Sr, Y and Zn in the human body. *Annales medicinae Experimentalis et Biologie (Finland) 50*, 99 -162
23. Holm, W., Schneider, H.-J., and Anke, M. (1971) Der Mineralstoffgehalt des Ejakulates und seine Beziehung zum Mengen- und Spurenelementgehalt von Prostate, Samenblase, Nebenhoden und Hoden. *Arch. Exper. Vet. Med. 25*, 811-815
24. Tohno, S., Kobayashi, M., Shimizu, H., Tohno, Y., Suwannahoy, P. et al. (2009) Age-related changes of the concentrations of select elements in the prostates of Japanese. *Biol. Trace Elem. Res. 127*, 211-227
25. Yamagata, N. (1962) The concentration of common cesium and rubidium in human body. *J. Radiation Res. 3*, 9-30
26. Marezynska, A., Kulpa, J., and Lenko, J. (1983) The concentration of zinc in relation to fundamental elements in the diseases human prostate. *Int. Urol. Nephrol. 15*, 257-265
27. Schneider, H.-J., Anke, M., and Holm, W. (1970) The inorganic components of testicle, epididymis, seminal vesicle, prostate and ejaculate of young men. *Int. Urol. Nephrol. 2*, 419-427
28. Soman, S.D., Joseph, K.T., Raut, S.J., Mulay, G.D., Parameswaran, M. et al. (1970) Studies of major and trace element content in human tissues. *Health Phys. 19*, 641-656
29. Guntupalli, J.N.R., Padala, S., Gummuluri, A.V.R.M., Muktineni, R.K., Byreddy, S.R. et al. (2007) Trace elemental analysis of normal, benign hypertrophic and cancerous tissues of the prostate gland using the particle-induced X-ray emission technique. *Eur. J. Cancer Prev. 16(2)*, 108-115
30. Hienzsch, E., Schneider, H.-J., and Anke, M. (1970) Vergleichende Untersuchungen zum Mengen- und Spurenelementgehalt der normalen Prostata, des Prostataadenoms und des Prostatakarzinoms. *Zeitschrift für Urologie und Nephrologie* 63, 543-546
31. Kwiatek, W.M., Banas, A., Gajda, M., Ga³ka, M., Pawlicki, B. et al. (2005) Cancerous tissues analyzed by SRIXE. *Journal of Alloys and Compounds 401*, 173-177
32. Picurelli, L., Olcina, P.V., Roig, M.D., and Ferrer, J. (1991) Determination of Fe, Mg, Cu, and Zn in normal and pathological prostatic tissue. *Actas Urol. Esp. 15*, 344-350
33. Yaman, M., Atici, D., Bakirdere, S., and Akdeniz, I. (2005) Comparison of trace metal concentrations in

malignant and benign human prostate. *J. Med. Chem. 48*, 630-634

34. Banacœ, A., Kwiatek, W.M., and Zaj¹c, W. (2001) Trace element analysis of tissue section by means of synchrotron radiation: the use of GNUPLOT for SPIXE spectra analysis. *Journal of Alloys and Compounds 328(1-2),* 135–138

35. Zaichick, V. (1997) Sampling, sample storage and preparation of biomaterials for INAA in clinical medicine, occupational and environmental health. In: *Harmonization of Health-Related Environmental Measurements Using Nuclear and Isotopic Techniques*. International Atomic Energy Agency, Vienna, 123-133

36. Zaichick, V. and Zaichick, S. (1997) A search for losses of chemical elements during freeze-drying of biological materials. *J. Radioanal. Nucl. Chem. 218 (2)*, 249-253

37. Zaichick, V. (2004) Losses of chemical elements in biological samples under the dry aching process. *Trace Elements in Medicine 5(3)*, 17-22 (in Russian)

38. Zaichick ,V. (1995) Applications of synthetic reference materials in the medical Radiological Research Centre. *Fresenius J. Anal. Chem. 352*, 219-223

39. Zaichick, S. and Zaichick V. (2010) The effect of age and gender on 37 chemical element contents in scalp hair of healthy humans. *Biol. Trace Elem. Res. 134(1)*, 41-54

40. Györkey, F., Min, K.-W., Huff, J.A., and Györkey, P. (1967) Zinc and magnesium in human prostate gland: Normal, hyperplastic, and neoplastic. *Cancer Res. 27*, 1349-1353

41. Saltzman, B.E., Gross, S.B., Yeager, D.W., Meiners, B.G., and Gartside, P.S. (1990) Total body burdens and tissue concentrations of lead, cadmium, copper, zinc, and ach in 55 human cadavers. *Environmental Research 52*, 126-1453

42. Zaichick, V., Zaichick, S. (2014) Relations of the neutron activation analysis data to morphometric parameters in pediatric and nonhyperplastic young adult prostate glands. *Advances in Biomedical Science and Engineering 1(1)*, 26-42

43. Shan, W., Zhong, W., Swanlund, J., and Oberley, T.D. (2012) Oxidative Stress in Prostate Cancer. In: *Oxidative Stress in Cancer Biology and Therap*, Part *4*, Chapter *15*, 301-331

44. Iizuka, S., Taniguchi, N., and Makita, A. (1984) Enzyme-linked immunosorbent assay for human manganese-containing superoxide dismutase and its content in lung cancer. *J. Natl. Cancer Inst. 72,* 1043 -1049

45. Ishikawa, M., Yaginuma, Y., Hayashi, H., Shimizu, T., Endo, Y., et al. (1990) Reactivity of a monoclonal antibody to manganese superoxide dismutase with human ovarian carcinoma. *Cancer Res. 50*, 2538-2542

46. Hu, Y., Rosen, D.G., Zhou, Y., Feng, L., Yang, G. et al. (2005) Mitochondrial manganese-superoxide dismutase expression in ovarian cancer. *Journal of Biological Chemistry 280*, 39485-39492

47. Nishida, S., Akai, F., Iwasaki, H., Hosokawa, K., Kusunoki, T., et al. (1993) Manganese superoxide dismutase content and localization in human thyroid tumors. *The Journal of Patholog 169(3)*, 341-345

48. Oberley, T. D., Sempf, J. M., Oberley, M. J., McCormick, M. L.,Muse, K. E., et al. (1994)

Immunogold analysis of antioxidant enzymes in human renal cell carcinoma. *Virchows Arch*. *424*, 155 -164

49. Cobbs, C.S., Levi, D.S., Aldape, K., and Israel, M.A. (1996). Manganese superoxide dismutase expression in human central nervous system tumors. *Cancer Res*. *56*, 3192-3195

50. Izutani, R., Asano, S., Imano, M., Kuroda, D., Kato, M., et al. (1998) Expression of manganese superoxide dismutase in esophageal and gastric cancers. *J. Gastroenterol*. *33*, 816-822

51. Mirand, A., Jansse, L., Bosma, C.B.,,Van Duij, W., Oostendorp-van de Rui M.M., et al. (2000) Superoxide dismutases in gastric and esophageal cancer and the prognostic impact in gastric cancer. *Clin. Cancer Res. 6*, 3183-3192

52. Kahlos, K., Pitkänen, S., Hassinen, I., Linnainmaa, K., and Kinnula V.L. (1999) Generation of reactive oxygen species by human mesothelioma cells. *British Journal of Cancer 80(1-2)*, 25-31

53. Hasegawa, Koshikawa, Takahashi, Hachiya, Furukawa, et al. (2008) Alterations in manganese, copper, and zinc contents, and intracellular status of the metal-containing superoxide dismutase in human mesothelioma cells. *J Trace Elem Med Biol 22(3)*, 248-255

54. Oberley, L.W. and Oberley, T.D. (1998) Oxyradicals and malignant transformation. In: *Advances in molecular and cellular biology*, McCord. Ed., JAI Press, 45-69

55. Janssen, A.M.L., Bosman, C.B., Kruidenier, L., Griffioen, G., Lamers, C.B.H.W., et al. (1999) Superoxide dismutases in the human colorectal cancer sequence. *J. Cancer Res. Clin. Oncol*. *125*, 327-335

56. Tsanou, E., Ioachim, E., Briasoulis, E., Damala, K., Charchanti, A., et al. (2004) Immunohistochemical expression of superoxide dismutase (MnSOD) antioxidant enzyme in invasive breast carcinoma. *Hist. Histopathol*. *19*, 807-813

57. Oberley, TD. (2002). Oxidative damage and cancer. *Am. J. Path*. *160*, 403-408

58. Hasegawa, Koshikawa, Takahashi, Hachiya, Furukawa, et al. (2008) Alterations in manganese, copper, and zinc contents, and intracellular status of the metal-containing superoxide dismutase in human mesothelioma cells. *J Trace Elem Med Biol 22(3)*, 248-255

59. Maschkovsky, M.D. (2005) The sedatives. In: *The Medicaments*, 15th Ed., Novaya Volna, Moscow, 72-86