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# Distinguishing malignant from benign prostate using Br, Ca, K, Mg, Mn, and Na content in prostatic tissue

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## Abstract

Contents of Br, Ca, K, Mg, Mn, and Na in normal (n=37), benign hypertrophic (n=27) and cancerous tissues (n=23) of the human prostate gland were investigated by non-destructive instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR). Mean values ± standard error of mean (M ± SEM) for mass fraction (mg/kg on dry mass basis) of chemical element in the normal tissue were as follows: Br 32.9 ± 3.6, Ca 2280 ± 178, K 11211 ± 414, Mg 1118 ± 76, Mn 1.24 ± 0.07, and Na 11100 ± 408, respectively. It was observed that in benign hypertrophic tissues the levels of Br, Ca, Mg, Mn, and Na were equal to those in normal prostate tissues while the level of K was significantly higher. By contrast, the levels Ca, Mg, K, and Na were significantly lower and those of Br and Mn were significantly higher in cancerous tissues than in normal and BPH tissues. The Br, Ca, Mg, and Mn mass fractions were the most informative indicators for distinguishing malignant from benign prostate with sensitivity, specificity, and accuracy in the ranges 91-100%, 92-100%, and 93-100%, respectively. Obtained data allowed us to adequately evaluate the importance of chemical element content for the diagnosis of prostate cancer.

## Introduction

The prostate gland may be a source of many health problems in men past middle age, the most common being benign prostatic hyperplasia (BPH), and prostatic carcinoma (PCa). BPH is a noncancerous enlargement of the prostate gland leading to obstruction of the urethra and can significantly impair quality of life [1]. The prevalence of histological BPH is found in approximately 50-60% of males age 40-50, in over 70% at 60 years old and in greater than 90% of men over 70 [2,3]. In many Western industrialized countries, including North America, PCa is the most frequently diagnosed form of noncutaneous malignancy in males and, except for lung cancer, is the leading cause of death from cancer [49]. Although the etiology of BPH and PCa is unknown, some electrolytes and trace elements have been highlighted in the literature in relation to the development of these prostate diseases [10-29].

Electrolytes and trace elements have essential physiological functions such as maintenance and regulation of cell function and signalling, gene regulation, activation or inhibition of enzymatic reactions, neurotransmission, and regulation of membrane function. Essential or toxic (mutagenic, carcinogenic) properties of chemical elements depend on tissue-specific need or tolerance, respectively [30]. Excessive accumulation, deficiency or an imbalance of the chemical elements may disturb the cell functions and may result in cellular degeneration, death and malignant transformation [31].

In reported studies significant changes of chemical element contents in hyperplastic and cancerous prostate in comparison with those in the normal prostatic tissue were observed [32-56]. Moreover, a significant informative value of Zn content as a tumor marker for PCa diagnostics was shown by us [57,58]. Hence it is possible that besides Zn, some other chemical elements also can be used as tumor markers for distinguish between benign and malignant prostate.

Current methods applied for measurement of chemical element contents in samples of human tissue include a number of methods. Among these methods the instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR) is a non-destructive and one of the most sensitive techniques. It allows measure the chemical element contents in a few milligrams tissue without any treatment of sample. Analytical studies of the Br, Ca, K, Mg, Mn, and Na contents in normal, BPH and PCa tissue were done by us using INAA-SLR [15,21,28,50,55]. Nondestructive method of analysis avoids the possibility of changing the content of chemical elements in the studied samples [59-62], which allowed for the first time to obtain reliable results. In particular, it was shown that the average mass fraction of Ca in BPH tissue does not differ from normal level [54], but in PCa tissues it is 3.4 times lower than in healthy prostatic tissue [50]. Obtained results formed the basis for a new method for differential diagnosis of BPH and PCa, the essence of which was to determine the content of Ca in the material of transrectal needle biopsy of prostate indurated site.

Therefore, the present study had three aims. The main objective was to assess the Br, Ca, K, Mg, Mn, and Na contents in intact prostate of healthy men aged over 40 years and in the prostate gland of age-matched patients, who had either BPH or PCa using INAA-SLR analysis. The second aim was to compare the levels of chemical elements in normal,

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hyperplastic, and cancerous prostate, and the third aim was to evaluate the chemical element content for diagnosis of prostate cancer.

All studies were approved by the Ethical Committees of the Medical Radiological Research Centre, Obninsk.

## Material and methods

### Samples

All patients studied (n=50) 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 has been confirmed by clinical and morphological results obtained during studies of biopsy and resected materials. The age of 27 patients with BPH ranged from 56 to 78 years, the mean being 67.3 ± 5.6 (M ± SD) years. The 23 patients aged 51-78 suffered from PCa. Their mean age was 67.3 ± 8.6 (M ± SD) years.

Intact (Norm) prostates were removed at necropsy from 37 men aged 41-79 who had died suddenly. Their mean age was 55 ± 11 (M ± SD) years. The majority of deaths were due to trauma. Tissue samples were collected from the peripheral zone of dorsal and lateral lobes of their prostates, within 2 days of death and then the samples were divided into two portions. One was used for morphological study while the other was intended for chemical element analysis. A histological examination was used to control the age norm conformity, as well as to confirm the absence of microadenomatosis and latent cancer [15,21,28].

### 4Sample preparation, instrumentation, methods and certified reference materials

Details of sample preparation, the relevant nuclear reactions, radionuclides, gamma energies, methods of analysis and the results of quality control were presented in our earlier publications concerning the chemical elements of human prostate tissue investigated by INAA-SLR [15,21,28,50,55,63].

### Computer programs and statistic

A dedicated computer program for INAA mode optimization was used [64]. 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 was calculated for chemical element mass fraction in normal, benign hyperplastic and cancerous prostate tissue. The difference in the results between BPH and Norm, PCa and Norm, and PCA and BPH was evaluated by Student's *t*-test. For the construction of "individual data sets for Br, Ca, K, Mg, Mn, and Na mass fraction n normal, benign hypertrophic and cancerous prostate" diagrams the Microsoft Office Excel software was also used.

## Results

Table 1 depicts our data for six chemical elements in ten sub-samples of certified reference material (CRM) IAEA H-4 (animal muscle) and the certified values of this material.

Table 2 presents certain statistical parameters (arithmetic mean,

**Table 1.** NAA-SLR data of chemical element contents in reference material IAEA H-4 (animal muscle) compared to certified values (mg/kg, dry mass basis).

| Element | IAEA H-4 (animal muscle) | This work results |
|---|---|---|
| | 95% confidence interval | Mean ± SD |
| Br | 3.5 – 4.7[a] | 5.0 ± 0.9 |
| Ca | 163 – 213[a] | 238 ± 59 |
| K | 15300 – 16400[a] | 16200 ± 3800 |
| Mg | 990 – 1110[a] | 1100 ± 190 |
| Mn | 0.48 – 0.55[b] | 0.55 ± 0.11 |
| Na | 1930 – 2180[a] | 2190 ± 140 |

Mean – arithmetical mean, SD – standard deviation, [a]- certified values, [b] – 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, benign hyperplastic (BPH), and cancerous (PCa) prostate.

| Tissue | Parameter | Mean | SD | SEM | Min | Max | Median | P 0.025 | P 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 |
| BPH | Br | 30.4 | 18.4 | 3.6 | 5.5 | 77 | 25.6 | 5.75 | 66.7 |
| n=27 | Ca | 2032 | 547 | 165 | 1168 | 2762 | 1898 | 1173 | 2757 |
| | K | 14472 | 2454 | 740 | 11683 | 20519 | 13552 | 12025 | 19744 |
| | Mg | 1201 | 276 | 83 | 687 | 1585 | 1263 | 749 | 1552 |
| | Mn | 1.19 | 0.31 | 0.09 | 0.80 | 1.80 | 1.20 | 0.80 | 1.73 |
| | Na | 11612 | 2882 | 869 | 7762 | 15503 | 10564 | 7893 | 15400 |
| PCa | Br | 115 | 45 | 9.5 | 11.3 | 193 | 115 | 13.1 | 184 |
| n=23 | Ca | 674 | 193 | 58 | 382 | 952 | 751 | 411 | 931 |
| | K | 8542 | 1672 | 504 | 6047 | 11833 | 8784 | 6270 | 11402 |
| | Mg | 346 | 193 | 61 | 136 | 632 | 313 | 138 | 624 |
| | Mn | 7.0 | 4.5 | 1.4 | 1.00 | 16.2 | 5.80 | 1.33 | 15.0 |
| | Na | 7511 | 2133 | 643 | 3913 | 12239 | 7228 | 4420 | 11539 |

M – arithmetic mean, SD – standard deviation, SEM – standard error of mean, Min – minimum value, Max – maximum value, P 0.025 – percentile with 0.025 level, P 0.975 – percentile with 0.975 level.

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 mass fractions in normal, benign hypertrophic and cancerous prostate.

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

The comparison of our results with published data for Br, Ca, K, Mg, Mn, and Na mass fraction in normal, benign hypertrophic and cancerous prostate is shown in Table 4.

Table 5 contains parameters of the importance (sensitivity, specificity and accuracy) of Br, Ca, Mg, and Mn mass fraction for the diagnosis of PCa calculated in this work.

Figure 1 depicts individual data sets for Br, Ca, K, Mg, Mn, and Na mass fraction in all samples of normal, benign hypertrophic and cancerous prostate.

## Discussion

As was shown by us [15,21,28] the use of CRM IAEA H-4 as a certified reference material for the analysis of samples of prostate tissue can be seen as quite acceptable. Good agreement of the Br, Ca, K, Mg, Mn, and Na contents analyzed by INAA-SLR with the certified data of CRM IAEA H-4 (Table 1) indicates an acceptable accuracy of the results obtained in the study of chemical elements of the prostate presented in Tables 2–4.

The mean values and all selected statistical parameters were calculated for six (Br, Ca, K, Mg, Mn, and Na) chemical element mass fractions (Table 2). The mass fraction of these chemical elements were measured in all, or a major portion of normal prostate samples. The masses of BPH and PCa samples varied very strong from a few milligrams (sample from needle biopsy material) to 100 mg (sample from resected material). Therefore, in BPH and PCa prostates mass fractions of Br were measured in all samples, while mass fractions of Ca, K, Mg, Mn, and Na were determined in 22 samples (11 and 11 samples, respectively).

From Table 3, it is observed that in benign hypertrophic tissues the mass fractions of Br, Ca, Mg, Mn, and Na not differ from normal levels while the mass fraction of K is significantly ($p$=0.0014) higher. In cancerous tissue the mass fractions of Ca ($p$=0.000000003), K

**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, benign hyperplastic (BPH), and cancerous (PCa) prostate.

| Element | Prostatic tissue | | | Ratios, $p$ (Student's $t$-test) | | |
|---|---|---|---|---|---|---|
| | Normal 41-79 year n=37 | BPH 56-78 year n=27 | Cancer 51-78 year n=23 | BPH to Normal | Cancer to Normal | Cancer to BPH |
| Br | 32.9 ± 3.6 | 30.4 ± 3.6 | 115 ± 10 | 0.92 | 3.50[b] | 3.78[b] |
| Ca | 2280 ± 178 | 2032 ± 165 | 674 ± 58 | 0.89 | 0.30[b] | 0.33[b] |
| K | 11211 ± 414 | 14472 ± 740 | 8542 ± 504 | 1.29[b] | 0.76[b] | 0.59[b] |
| Mg | 1118 ± 76 | 1201 ± 83 | 346 ± 61 | 1.07 | 0.31[b] | 0.29[b] |
| Mn | 1.24 ± 0.07 | 1.19 ± 0.09 | 7.0 ± 1.4 | 0.96 | 5.65[a] | 5.88[a] |
| Na | 11100 ± 408 | 11612 ± 869 | 7511 ± 643 | 1.05 | 0.68[b] | 0.65[a] |

*M* arithmetic mean, *SEM* standard error of mean,
Statistically significant difference: [a] – $p$<0.01, [b] – $p$<0.001.

**Table 4.** Median, minimum and maximum value of means of chemical element contents (mg/kg, dry mass basis) in normal, benign hyperplastic (BPH), and cancerous (PCa) prostate according to data from the literature in comparison with our results.

| c | Element | Published data [Reference] | | | This work results |
|---|---|---|---|---|---|
| | | Median of means ($n$)* | Minimum of means M or M ± SD, ($n$)** | Maximum of means M or M ± SD, ($n$)** | M ± SD |
| Normal | Br | 14 (3) | 12 ± 8 (4) [32] | 21 (12) [33] | 32.9 ± 17.7 |
| | Ca | 1870(14) | 430 ± 120 (21) [34] | 7500 ± 12300 (57) [35] | 2280 ± 874 |
| | K | 9900(12) | 3840 (8) [36] | 12200 ± 1500 (8) [37] | 11211 ± 2071 |
| | Mg | 900(12) | 498 ± 172 (13) [35] | 2056 ± 476 (21) [38] | 1118 ± 396 |
| | Mn | 6.0 (11) | <0.47 (12) [33] | 106 ± 18 (5) [39] | 1.24 ± 0.32 |
| | Na | 6100(7) | 23 ± 26 (13) [35] | 13700 ± 3500 (4) [40] | 11100 ± 2159 |
| BPH | Br | 19.8 (2) | 18.0 ± 9.5 (27) [41] | 21.5 ± 13.0 (9) [42] | 30.4 ± 18.4 |
| | Ca | 2100 (7) | 600 ± 120 (2) [43] | 5100 ± 3200(9) [42] | 2032 ± 547 |
| | K | 7400 (6) | 1010 ± 95 (27) [41] | 12800 ± 1900 (43) [37] | 14472 ± 2454 |
| | Mg | 820 (6) | 566 ± 130 (25) [44] | 1560 ± 50 (10) [45] | 1201 ± 276 |
| | Mn | 10.8 (4) | 6.5 (-) [43] | 23 ± 13 (27) [41] | 1.19 ± 0.31 |
| | Na | 7800 (1) | 7800 (34) [46] | 7800 (34) [46] | 11612 ± 2882 |
| PCa | Br | 1.5 (1) | 1.5 ± 6.0 (27) [41] | 1.5 ± 6.0 (27) [41] | 115 ± 45 |
| | Ca | 2940 (7) | 1100 (4) [46] | 410000 ± 43000 (1) [43] | 674 ± 193 |
| | K | 3620 (4) | 740 ± 90 (27) [41] | 5600 (4) [46] | 8542 ± 1672 |
| | Mg | 935 (5) | 361 ± 174 (25) [44] | 1050 720 (11) [47] | 346 ± 193 |
| | Mn | 8.0 (4) | 2.74 ± 0.27 (1) [43] | 160 ± 22 (1) [39] | 7.0 ± 4.5 |
| | Na | 5100 (1) | 5100 (4) [46] | 5100 (4) [46] | 7511 ± 2133 |

*M* arithmetic mean, *SD* standard deviation, ($n$)* number of all references, ($n$)** number of samples

**Table 5.** Parameters of the importance (sensitivity, specificity and accuracy) of some chemical element mass fractions for the diagnosis of PCa (an estimation is made for "PCa or intact and BPH tissue").

| Element | Limit for PCa (M ± SD) mg/kg, dry mass basis | Sensitivity % | Specificity % | Accuracy % |
|---|---|---|---|---|
| Br | 70 mg/kg - Lower limit (M-SD) | 91 ± 6 | 97 ± 2 | 95 ± 2 |
| Ca | 1060 mg/kg - Upper limit (M+2SD) | 100-9 | 100-2 | 100-2 |
| Mg | 730 mg/kg - Upper limit (M+2SD) | 100-9 | 92 ± 4 | 93 ± 3 |
| Mn | 2.2 mg/kg - Lower limit (~M-SD) | 91 ± 9 | 100-2 | 98 ± 2 |

M - arithmetic mean, SD – standard deviation.

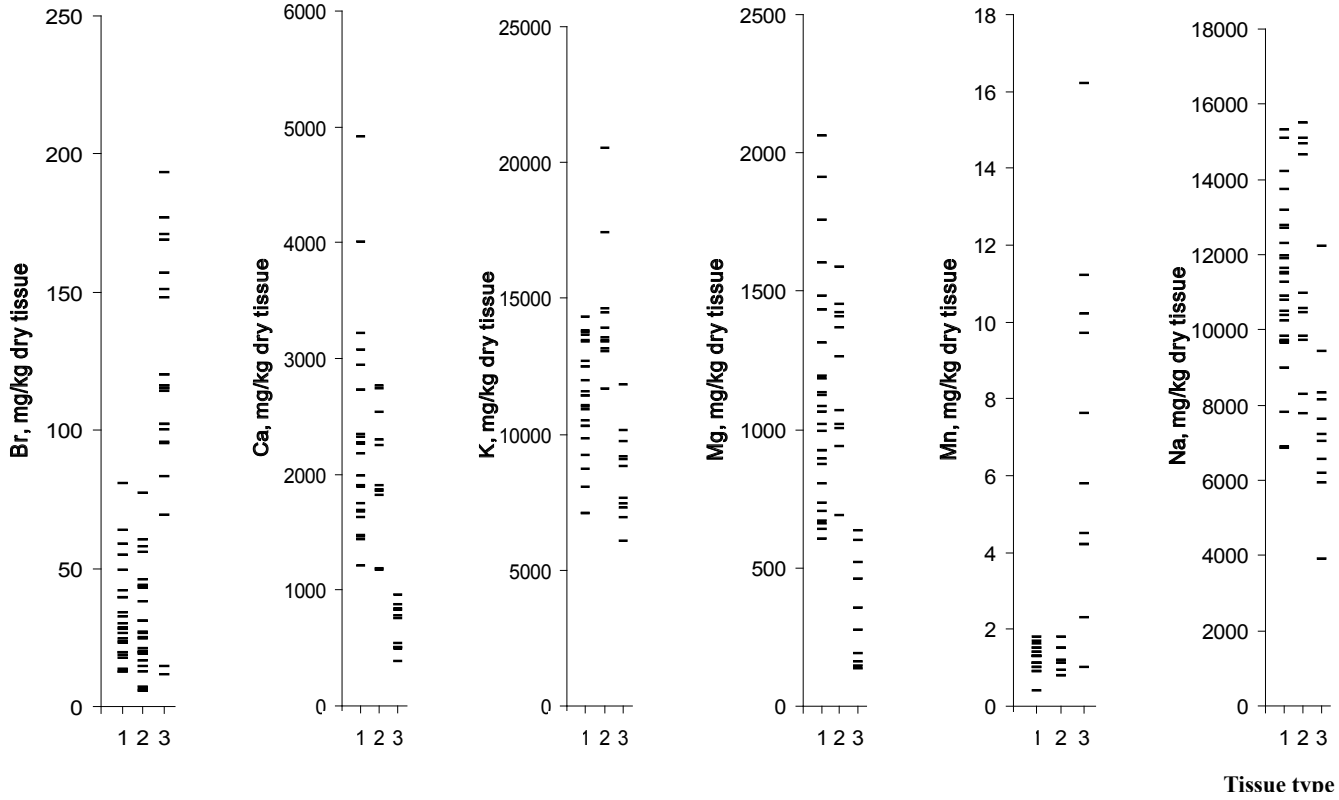


**Figure 1**. Individual data sets for Br, Ca, K, Mg, Mn, and Na mass fractions in samples of normal (1), benign hypertrophic (2) and cancerous prostate (3).

($p$=0.004), Mg $p$=0.000000005), and Na ($p$=0.0002) are significantly lower, and mass fractions of Br ($p$=0.000000007) and Mn ($p$=0.0017) are significantly higher than in normal tissues of the prostate. All these elements show similar variations in cancerous tissues when compared with benign hypertrophic tissues of the prostate. The mass fractions of Ca ($p$=0.000004), K ($p$=0.0000035), Mg $p$=0.00000015), and Na ($p$=0.0013) are significantly lower, and mass fractions of Br ($p$=0.000000004) and Mn ($p$=0.0016) are significantly higher than in benign hypertrophic tissues.

The results for all chemical element contents in the prostates of the control group (mean age 55 ± 11 years, range 41-79) are in accordance with our earlier findings in prostates of apparently healthy men aged 41-60 [15]. Values obtained for Br, Ca, K, Mg, Mn, and Na contents (Table 4) agree well with median of mean values cited by other researches for the human prostate [32-47]. Data of the literature also includes samples obtained from patients who died from different diseases. A number of values for chemical element mass fractions were not expressed on a dry mass basis in the cited literature. Therefore, we calculated these values using published data for water - 80% [45] and ash - 1% on wet mass basis [65] contents in the prostate of adult men. Our results for for Br, Ca, K, Mg, Mn, and Na are in accordance with the medians of earlier findings in benign hypertrophic tissues of prostate (Table 4). In cancerous prostate tissues our results were comparable with published data for Mg, Mn, and Na contents, some lover for Ca, some higher for K, and almost two orders of magnitude higher for Br (Table 4).

Analysis of chemical element mass fraction in prostate tissue could become a powerful diagnostic tool. To a large extent, the resumption of the search for new methods for early diagnosis of PCa was due to experience gained in a critical assessment of the limited capacity of the prostate specific antigen (PSA) serum test [66]. In addition to the PSA serum test and morphological study of needle-biopsy cores of the prostate, the development of other highly precise testing methods seems to be very useful. Experimental conditions of the present study were approximated to the hospital conditions as closely as possible. In BPH and PCa cases we analyzed a part of the material obtained from a puncture transrectal biopsy of the indurated site in the prostate. Therefore, our data allow us to evaluate adequately the importance of chemical element mass fraction for the diagnosis of PCa. As is evident from individual data sets (Figure 1), the Br, Ca, Mg, and Mn mass fraction are the most informative for a differential diagnosis.

For example, if 1060 mg/kg (M±2SD) is the value of Ca mass fraction assumed to be the upper limit for PCa (Figure 1) and an estimation is made for "PCa or intact and BPH tissue", the following values are obtained:

Sensitivity = {True Positives (TP)/[TP + False Negatives (FN)]} ·100% = 100-9%;

Specificity = {True Negatives (TN)/[TN + False Positives (FP)]} ·100% = 100-2%;

Accuracy = [(TP+TN)/(TP+FP+TN+FN)] ·100% = 100-2%.

The number of people (samples) examined was taken into account for calculation of confidence intervals [67]. In other words, if Ca mass fraction in a prostate biopsy sample does not exceed 1060 mg/kg, one could diagnose a malignant tumor with an accuracy 100-2%. Thus, using the Ca mass fraction-test makes it possible to diagnose cancer in 100-2%; cases (sensitivity). The same way parameters of the importance (sensitivity, specificity and accuracy) of Br, Mg, and Mn mass fraction for the diagnosis of PCa were calculated (Table 5).

It should be noted, however, that Br is a component of many tranquilizers. It is possible that the increase in Br content could be explained by uncontrolled use of tranquilizers in the group of PCa patients. Therefore, for diagnostic purposes, data for Br content should be used with caution.

## Conclusion

In this work, elemental analysis was carried out in the tissue samples of normal, benign hypertrophic, and carcinomatous prostates 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 benign hypertrophic tissues the contents of Br, Ca, K, Mg, Mn, and Na were equal to those in normal prostate tissues with the exception of higher K level. The contents of Ca, K, Mg, and Na were significantly lower and those of Br and Mn were significantly higher in cancerous tissues than in normal and BPH tissues. Finally, we propose to use the Ca, Mg, and Mn mass fraction in a needle-biopsy core as an accurate tool to diagnose prostate cancer. Further studies on larger number of samples are required to confirm our findings, to study the impact of the trace elements on prostate cancer etiology and to examine the long-term pathological outcome.

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## Competing interests

All other authors declare no competing interests.

## Authors' contributions

VZ was responsible for the study design, INAA-LLR analyses, and manuscript preparation. SZ was responsible for data collection, data entry, statistical analyses and assistance with manuscript preparation. Both authors read and approved of the final manuscript.

### References

1. Kirby RS (2000) The natural history of benign prostatic hyperplasia: what have we learned in the last decade? *Urology* 56: 3-6. [Crossref]
2. Roehrborn C, McConnell J (2002) Etiology, pathophysiology, epidemiology and natural history of benign prostatic hyperplasia. In: Walsh P, Retik A, Vaughan E, Wein A, editors. Campbell's Urology. 8th ed. Philadelphia: Saunders, p. 1297-1336.
3. Lepor H (2005) Pathophysiology of benign prostatic hyperplasia in the aging male population. *Rev Urol* 7 Suppl 4: S3-3S12. [Crossref]
4. Oliver SE, Gunnell D, Donovan JL (2000) Comparison of trends in prostate-cancer mortality in England and Wales and the USA. *Lancet* 355: 1788-1789. [Crossref]
5. Kumar RJ, Barqawi AB, Crawford ED (2004) Epidemiology of prostate cancer. Business Briefing: *US Oncology Review*: 1-6.
6. Maddams J, Brewster D, Gavin A, Steward J, Elliott J, et al. (2009) Cancer prevalence in the United Kingdom: estimates for 2008. *Br J Cancer* 101: 541-547. [Crossref]
7. Lutz JM, Francisci S, Mugno E, Usel M, Pompe-Kirn V, et al. (2003) Cancer prevalence in Central Europe: the EUROPREVAL Study. *Ann Oncol* 14: 313-322. [Crossref]
8. Möller T, Anderson H, Aareleid T, Hakulinen T, Storm H, et al. (2003) Cancer prevalence in Northern Europe: the EUROPREVAL study. *Ann Oncol* 14: 946-957. [Crossref]
9. De Angelis R, Grande E, Inghelmann R, Francisci S, Micheli A, et al. (2007) Cancer prevalence estimates in Italy from 1970 to 2010. *Tumori* 93: 392-397. [Crossref]
10. Waalkes MP, Rehm S (1994) Cadmium and prostate cancer. *J Toxicol Environ Health* 43: 251-269. [Crossref]
11. Zaichick V, Zaichick S (1999) Role of zinc in prostate cancerogenesis. In: Anke M, et al., editors. Mengen und Spurenelemente. 19. Arbeitstagung. Jena: Friedrich-Schiller-Universitat; p.104-115.
12. Platz EA, Helzlsouer KJ (2001) Selenium, zinc, and prostate cancer. *Epidemiol Rev* 23: 93-101. [Crossref]
13. Zaichick V (2004) INAA and EDXRF applications in the age dynamics assessment of Zn content and distribution in the normal human prostate. *J Radioanal Nucl Chem* 262: 229-234.
14. Gray MA, Centeno JA, Slaney DP, Ejnik JW, Todorov T, et al. (2005) Environmental exposure to trace elements and prostate cancer in three New Zealand ethnic groups. *Int J Environ Res Public Health* 2: 374-384. [Crossref]
15. Zaichick S, 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.
16. Zaichick S, 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: 827-833. [Crossref]
17. Zaichick S, Zaichick V (2011) The Br, Fe, Rb, Sr, and Zn content and interrelation in intact and morphologic normal prostate tissue of adult men investigated by energy dispersive X-ray fluorescent analysis. *X-Ray Spectrom* 40: 464-469.
18. Zaichick V, Nosenko S, Moskvina I (2012) The effect of age on 12 chemical element contents in the intact prostate of adult men investigated by inductively coupled plasma atomic emission spectrometry. *Biol Trace Elem Res* 147: 49-58. [Crossref]
19. Zaichick S, Zaichick V, Nosenko S, Moskvina I (2012) Mass Fractions of 52 Trace Elements and Zinc Trace Element Content Ratios in Intact Human Prostates Investigated by Inductively Coupled Plasma Mass Spectrometry. *Biol Trace Elem Res* 149: 171-183. [Crossref]
20. Zaichick V, Zaichick S (2014) Age-related histological and zinc content changes in adult nonhyperplastic prostate glands. *Age (Dordr)* 36: 167-181. [Crossref]
21. Zaichick V, Zaichick S2 (2014) INAA application in the assessment of chemical element mass fractions in adult and geriatric prostate glands. *Appl Radiat Isot* 90: 62-73. [Crossref]
22. Zaichick V, Zaichick S (2014) Determination of trace elements in adults and geriatric prostate combining neutron activation with inductively coupled plasma atomic emission spectrometry. *Open J Biochem* 1: 16-33.
23. Zaichick V, 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(2): 383-397.
24. 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: 44-60.[Crossref]

25. Zaichick V, Zaichick S (2015) Dietary intake of minerals and prostate cancer: insights into problem based on the chemical element contents in the prostate gland. *J Aging Res Clin Practice* 4: 164-171.

26. Zaichick V, Zaichick S (2015) Global contamination from uranium: insights into problem based on the uranium content in the human prostate gland. *J Environ Health Sci* 1: 1-5.

27. Zaichick V, Zaichick S (2016) Variations in concentration and distribution of several androgen-dependent and -independent trace elements in nonhyperplastic prostate gland tissue throughout adulthood. *J Androl Gynaecol* 4: 1-10.

28. Zaichick V, Zaichick S (2016) Age-related changes in concentration and histological distribution of Br, Ca, Cl, K, Mg, Mn, and Na in nonhyperplastic prostate of adults. *Europ J Biol Med Sci Res* 4: 31-48.

29. Zaichick V, Zaichick S (2016) Variations in concentration and histological distribution of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn in nonhyperplastic prostate gland throughout adulthood. *Jacobs J Cell Mol Biol* 2, 011: 1-16.

30. Zaichick V (2006) Medical elementology as a new scientific discipline. *J Radioanal Nucl Chem* 269: 303-309.

31. Schwartz MK (1975) Role of trace elements in cancer. *Cancer Res* 35(11 Pt. [Crossref]

32. Kubo H, Hashimoto S, Ishibashi A (1976) Simultaneous determinations of Fe, Cu, Zn, and Br concentrations in human tissue sections. *Med Phys* 3: 204-209. [Crossref]

33. Forssén 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. *Ann Med Exp Biol Fenn* 50: 99-162. [Crossref]

34. Holm W, Schneider HJ, Anke M (1971) [Mineral content of the ejaculate and its relationship to larger amounts and trace elements in the prostate, seminal vesicles, epididymis and testis]. *Arch Exp Veterinarmed* 25: 811-815. [Crossref]

35. 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. [Crossref]

36. Leitão RG, Palumbo A, Souza PAVR, Pereira GR, Canellas CGL, et al. (2014) Elemental concentration analysis in prostate tissues using total reflection X-ray fluorescence. *Radiation Physics and Chemistry* 95: 62-64

37. MarczyÅ„ska A, Kulpa J, LeÅ„ko J (1983) The concentration of zinc in relation to fundamental elements in the diseased human prostate. *Int Urol Nephrol* 15: 257-265. [Crossref]

38. Schneider H-J, Anke M, Holm W (1970) The inorganic components of testicle, epididymis, seminal vesicle, prostate and ejaculate of young men. *Int Urol Nephrol* 2: 419-427.

39. Banas A, Kwiatek WM, Zajac W (2001) Trace element analysis of tissue section by means of synchrotron radiation: the use of GNUPLOT for SPIXE spectra analysis. *J Alloys Compou* 328: 135-138.

40. Soman SD, Joseph KT, Raut SJ, Mulay CD, Parameshwaran M, et al. (1970) Studies on major and trace element content in human tissues. *Health Phys* 19: 641-656. [Crossref]

41. Guntupalli JNR, Padala S, Gummuluri AVRM, Muktineni RK, Byreddy SR, 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: 108-115. [Crossref]

42. Leitão RG, Palumbo AJ, Correia R C, Souza PAVR, Canellas CGL, et al. (2009) Elemental concentration analysis in Benign Prostatic Hyperplasia tissue cultures by SR-TXRF. Brazilian Synchrotron Light Laboratory. *Activity Report* 1-2.

43. Kwiatek WM, Banas A, Gajda M, Galka M, Pawlicki B, et al. (2005) Cancerous tissues analyzed by SRIXE. *Journal of Alloys and Compounds* 401: 173-177.

44. Picurelli L, Olcina PV, Roig MD, Ferrer J (1991) [Determination of Fe, Mg, Cu, and Zn in normal and pathological prostatic tissue]. *Actas Urol Esp* 15: 344-350. [Crossref]

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

46. Hienzsch E, Schneider H-J, 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.

47. Yaman M, Atici D, Bakirdere S, Akdeniz I (2005) Comparison of trace metal concentrations in malign and benign human prostate. *J Med Chem* 48: 630-634. [Crossref]

48. Zaichick V, Zaichick S (2015) Differences and relationships between morphometric parameters and zinc content in nonhyperplastic and hyperplastic prostate glands. British *J Med Med Res* 8: 692-706.

49. Zaichick V, Zaichick S (2016) Trace element contents in adenocarcinoma of human prostate investigated by energy dispersive X-ray fluorescent analysis. *J Adenocarcinoma* 1: 1-7.

50. Zaichick V, Zaichick S (2016) The Bromine, Calcium, Potassium, Magnesium, Manganese, and Sodium Contents in Adenocarcinoma of Human Prostate Gland. *J Hematol Oncol Res* 2: 1-12.

51. Zaichick V, Zaichick S (2016) Trace element contents in adenocarcinoma of the human prostate gland investigated by neutron activation analysis. *Canc Res Oncol* 1: 1-10.

52. Zaichick V, Zaichick S (2016) Prostatic tissue levels of 43 trace elements in patients with prostate adenocarcinoma. *Canc Clin Oncol* 5: 79-94.

53. Zaichick V, Zaichick S (2016) Chemical elemental content / Calcium ratios in tissues of human hyperplastic prostate gland. *J Appl Lif Sci Int* 4: 1-11.

54. Zaichick V, Zaichick S, Davydov G (2015) Differences between chemical element contents in hyperplastic and nonhyperplastic prostate glands investigated by neutron activation analysis. *Biol Trace Elem Res* 164: 25-35. [Crossref]

55. Zaichick V, Zaichick S (2016) Prostatic tissue level of some major and trace elements in patients with BPH. Jacobs Journal of Nephrology and Urology 3(1): 025, 1-10.

56. Zaichick V, Zaichick S (2016) Levels of 43 Trace Elements in Hyperplastic Prostate Tissues. *British J Med Med Res* 15: 1-12.

57. Zaichick VYe, Sviridova TV, Zaichick SV (1997) Zinc in the human prostate gland: normal, hyperplastic and cancerous. *Int Urol Nephrol* 29: 565-574. [Crossref]

58. Zaichick S, Zaichick V (2012) Trace elements of normal, benign hypertrophic and cancerous tissues of the human prostate gland investigated by neutron activation analysis. *Appl Radiat Isot* 70: 81-87. [Crossref]

59. 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. Vienna: IAEA123-133.

60. Zaichick V, Zaichick S (1996) Instrumental effect on the contamination of biomedical samples in the course of sampling. *The J Analy Chem* 51: 1200-1205.

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

62. Zaichick V (2004) Losses of chemical elements in biological samples under the dry aching process. *Trace Elements in Med* 5: 17-22.

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

64. Korelo AM, Zaichick V (1993) Software to optimize the multielement INAA of medical and environmental samples. In: Activation Analysis in Environment Protection. Dubna, Moscow Region, Russia: Joint Institute for Nuclear Research, p.326–332.

65. Saltzman BE, Gross SB, Yeager DW, Meiners BG, Gartside PS (1990) Total body burdens and tissue concentrations of lead, cadmium, copper, zinc, and ash in 55 human cadavers. *Environ Res* 52: 126-145. [Crossref]

66. Catalona WJ (1996) Clinical utility of measurements of free and total prostate-specific antigen (PSA): a review. *Prostate* Suppl 7: 64-69. [Crossref]

67. Genes VS (1967) Simple methods for cybernetic data treatment of diagnostic and physiological studies. Moscow: Nauka.