Intracellular Zinc Excess as One of the Main Factors in the Etiology of Prostate Cancer

Vladimir Zaichick[1,*], Sofia Zaichick[1,2] and Sinclair Wynchank[3]

[1]*Radionuclide Diagnostics Department, Medical Radiological Research Centre, Korolyev Str. 4, Obninsk 249036, Kaluga Region, Russia*

[2]*Department of Medicine, University of Illinois College of Medicine, Chicago, IL 60612, USA*

[3]*Strategic Health Innovation Partnerships, Medical Research Council, Tygerberg, 7505, Western Cape, South Africa*

Abstract: Numerous studies show that prevalence of prostate cancer (PCa) drastically increases with age, these malignant tumours are mainly formed in the peripheral zone of the prostate gland, and a high intake of red meat is associated with a statistically significant elevation in risk of PCa. The factors which cause all these well-specified features of the PCa are currently unclear. Here we describe one factor which can play an important role in etiology of malignant transformation of the prostate and is connected with the above-mentioned features of PCa. It is hypothesized that the prostatic intracellular Zn concentrations are probably one of the most important factors in the etiology of PCa. For an endorsement of our standpoint the estimation of changes of intracellular Zn concentrations over males' lifespan was obtained using morphometric and Zn content data for the peripheral zone of prostate tissue, as well as Zn concentration in prostatic fluid. It was shown that the Zn concentrations in prostatic cells for men aged over 45 years are 10-fold higher than in those aged 18 to 30 years and this excessive accumulation of Zn may disturb the cells' functions, resulting in cellular degeneration, death or malignant transformation. We hypothesize this excessive intracellular Zn concentration in cells of the prostate gland periphery has previously unrecognized and most important consequences, associated with PCa.

Keywords: Human prostate gland, peripheral zone, prostatic cells, prostatic fluid, zinc, histological parameters, age-related changes in human prostate, prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is an internationally important medical problem that needs considerable attention as the disease is indolent and shows prolonged latency in association with high morbidity and mortality [1,2]. PCa is the most common male cancer in developed countries of Europe [3]. In North America, it is the most common cancer in males and, after lung cancer, is the leading cause of death in males from cancer [4,5].

Although carcinoma of the prostate is one of the most extensively studied malignancies, its causative factors remain unclear. The following well defined characteristics of PCa are relevant. Clinical PCa is a neoplasm of the aged for the prevalence of PCa drastically increases with age, being three orders of magnitude higher for the age group 40–79 years than for those younger than 39 years [6,7]. About 80% of PCa tumours are formed in the peripheral zone of the prostate gland [8,9]. A 120-fold difference in rates of prostate cancer among different countries suggests that environmental factors are of importance [3,10]. For example high consumption of red meat was associated with a statistically significant (two-fold) elevation in risk of PCa, compared to a low consumption [2, 11-14].

All these well-specified features of the PCa imply there is an etiological factor (or factors) for malignant transformation which may be located in, or selectively affects, the peripheral zone of the prostate gland. This effect increases with age and acts synergistically with a factor (or factors) linked to red meat consumption. In our opinion the trace element Zn can play a role in such an etiological intra-prostatic factor. The prostate differs markedly from other organs and tissues because of its exceptionally high Zn content [15]. In the normal prostate, Zn accumulates up to 10-fold higher levels than in other tissues [16-18]. Prostatic Zn levels depend on age and increase exponentially from puberty to young adulthood [19-21] and then continue increasing up to age 55-60 years [22-32]. The element is non-uniformly distributed within the glandular volume and the highest concentration of Zn is located in the prostate's peripheral zone [33-35]. Red meat is a main source of Zn intake for humans [36] and a high red meat intake provides elevated level of Zn in prostate tissue [17,18].

All these data concern the Zn content of the prostate gland. According to Deering *et al*. [37],

*Address correspondence to this author at the Medical Radiological Research Centre, Korolyev Str. 4, Obninsk 249036,Kaluga Region, Russia, Tel: (48439) 60289; Fax: (495) 956 1440; E-mail: vezai@obninsk.com

ISSN: 1927-7210 / E-ISSN: 1927-7229/16

prostatic tissue contains three main components: glandular epithelium (E), prostatic fluid contained in the glandular lumina (L), and fibromuscular tissue or stroma (S). In our previous studies it was shown that the Zn concentration in prostatic fluid is almost 3 times higher than in prostate tissue [38] and the prostatic fluid contained in glandular lumina is the main pool of prostatic Zn [39-44]. Moreover, it was found there was an increase of relative volume of prostatic fluid in the gland with age [44]. This raises a question about behavior of intracellular Zn concentration because the mainly intracellular Zn appears to be involved in the etiology of PCa.

There are two ways to investigate the prostatic intracellular Zn: directly and indirectly. The direct way includes measurement of Zn concentration in cells using different imaging techniques. One of the oldest such techniques is the dithizone Zn stain in prostate sections [34,45]. One of the newest methods used for this purpose is XRF analyses of Zn with scanning beam of synchrotron radiation induced X-ray emission [46]. The main disadvantages of all these techniques are the necessity to fix the tissue samples, using certain chemical compounds, and having to cut thin tissue sections. During these procedures some prostatic fluid is lost and so Zn redistribution in prostate tissue takes plase. Thus, results of such studies give only qualitative and often contradictory values of the Zn distribution [45].

In this study an indirect but quantitative way of intracellular Zn estimation in the prostate gland was used. The study's primary purpose was to obtain data about changes of morphometric and Zn concentration in the peripheral zone of nonhyperplastic prostate gland of apparently healthy males at different ages. The second aim was to collect and assess published relevant results of Zn concentration in prostatic fluid, which are needed to perform calculations, allowing an estimation of possible changes of Zn concentration in prostatic cells with age.

AGE-RELATED HISTOLOGICAL AND ZN CONCENTRATION CHANGES IN PROSTATE TISSUE

To clarify the age-related histological and Zn concentration changes in peripheral zones of nonhyperplastic prostate glands, a quantitative morphometric and four analytical methods of Zn determination were used. The prostates were obtained from autopsies of 99 subjects (European-Caucasian) aged 0–87 years who died mainly from sudden infant death syndrome, acute pulmonary etiologies (infants), pneumonia (children), and trauma (adults). Age ranges for subjects were divided into the seven groups listed in Table **1** and below. The available clinical data were reviewed for each subject. None of the subjects had a history of an intersex condition, endocrine disorder, neoplasm or other chronic disease that would affect the normal development of the prostate. None of the subjects was receiving medications known to affect prostate morphology, function or Zn content. All samples of peripheral zone of prostate glands were divided (with an anterior-posterior cross-section) into two portions. One tissue portion was reviewed by an anatomical pathologist while the other was used for the Zn concentration determination.

All histological slides prepared for use were examined by an anatomical pathologist to detect any focus of benign prostatic hyperplasia, carcinoma, or intraepithelial neoplasia, to exclude all these samples and those with artifacts and to select appropriate slides for further morphometric evaluation. Morphometric evaluations were then performed quantitatively using a stereological method [47]. The mean volume fractions of the stroma (S), glandular epithelium (E), and glandular lumina (L) in prostate tissue were determined for each prostate specimen. Details ofthe stereological method and procedures used here were presented in our earlier publications concerning quantitative morphometric studies of the human prostate gland [39-44].

After the samples intended for Zn determination were weighed, they were freeze-dried and homogenized. The Zn concentrations were estimated using four analytical methods: energy dispersive X-ray fluorescence (EDXRF), instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides (INAA-LLR), inductively coupled plasma atomic emission spectrometry (ICP-AES), and inductively coupled plasma mass spectrometry (ICP-MS). There was a good agreement between Zn concentration obtained by all these different methods and means of the four results for Zn concentration in every sample were used in the study. Details of the analytical methods and procedures used and appropriate details of relevant nuclear reactions, radionuclides, gamma-energies, wavelength, isotopes, spectrometers, spectrometer parameters and operating conditions have been presented in our earlier publications concerning the chemical elemental content of human prostate gland [19-21, 24-32]. For quality control of results, samples reference materials, certified

Table 1: Certain Statistical Characteristics of the Zn Concentration (mg/dm^3, Wet Tissue) and the Histologic Components (Fraction of dm^3, Wet Tissue) in the Peripheral Zone of Nonhyperplastic Prostate Gland of Males of Ages 0–87 Years

Age group no Age range Mean age n	Parameter	M	SD	SEM	Min	Max	Median	P0.025	P0.975
Group 1	Zn	32.6	26.7	4.9	11.9	155	27.1	12.9	84.8
0-13 years	Stroma	0.752	0.130	0.026	0.444	0.913	0.804	0.497	0.905
3.3 years	Epithelium	0.203	0.084	0.017	0.097	0.413	0.170	0.101	0.382
n=29	Lumen	0.045	0.047	0.009	0.003	0.158	0.029	0.0036	0.158
Group 2	Zn	91.0	43.6	19.5	40.5	160	81.0	44.2	153
14-20 years	Stroma	0.480	0.067	0.030	0.401	0.546	0.496	0.403	0.545
18.2 years	Epithelium	0.389	0.037	0.016	0.349	0.439	0.388	0.350	0.436
n=5	Lumen	0.131	0.049	0.022	0.093	0.211	0.105	0.094	0.204
Group 3	Zn	105	43.1	10.5	50.6	187	90.4	52.4	180
21-30 years	Stroma	0.460	0.121	0.032	0.267	0.709	0.457	0.280	0.696
26.4 years	Epithelium	0.384	0.096	0.026	0.254	0.559	0.385	0.259	0.550
n=16	Lumen	0.156	0.055	0.015	0.037	0.241	0.160	0.045	0.231
Group 4	Zn	127	51.5	14.7	50.7	216	115	59.9	213
31-40 years	Stroma	0.512	0.078	0.025	0.377	0.616	0.532	0.382	0.610
35.8 years	Epithelium	0.320	0.052	0.016	0.259	0.414	0.314	0.259	0.410
n=12	Lumen	0.168	0.034	0.011	0.103	0.209	0.164	0.112	0.209
Group 5	Zn	250	190	47.3	89.8	853	213	91.6	674
41-50 years	Stroma	0.450	0.086	0.025	0.339	0.574	0.433	0.340	0.572
45.4 years	Epithelium	0.323	0.055	0.016	0.253	0.389	0.312	0.253	0.388
n=16	Lumen	0.227	0.070	0.020	0.103	0.298	0.247	0.104	0.296
Group 6	Zn	216	137	41.0	42.5	475	202	48.3	448
51-60 years	Stroma	0.528	0.115	0.038	0.397	0.726	0.498	0.398	0.707
55.6 years	Epithelium	0.267	0.073	0.024	0.146	0.375	0.273	0.152	0.363
n=11	Lumen	0.205	0.093	0.031	0.097	0.343	0.194	0.097	0.340
Group 7	Zn	189	79.8	25.2	60.2	294	192	74.8	294
61-87 years	Stroma	0.608	0.085	0.032	0.516	0.767	0.603	0.518	0.751
68.8 years	Epithelium	0.256	0.059	0.022	0.146	0.319	0.273	0.156	0.316
n=10	Lumen	0.136	0.040	0.015	0.087	0.205	0.131	0.089	0.199
All groups	Zn	131	123	12.6	11.9	853	96.5	14.6	373
0-87 years	Stroma	0.576	0.164	0.018	0.267	0.913	0.539	0.339	0.892
31.0 years	Epithelium	0.289	0.100	0.011	0.097	0.559	0.288	0.125	0.467
n=99	Lumen	0.135	0.087	0.010	0.003	0.343	0.142	0.0051	0.298

n – number of samples, M – arithmetic mean, SD – standard deviation, SEM – standard error of mean, Min – minimum value, Max – maximum value, Med. – median, P0.025 – percentile with 0.025 level, P0.975 – percentile with 0.975 level.

by appropriate international bodies, were used [19-21, 24-32].

Table **1** presents basic statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, and percentiles with 0.025 and 0.975 levels) of the Zn concentrations (mg/dm^3, wet mass basis) and the histologic components (fraction of dm^3, wet tissue) in

peripheral zone of nonhyperplastic prostate glands of males in the age range 0–13 years (group 1), 14–20 years (group 2), 21–30 years (group 3), and 31–40 years (group 4), 41–50 years (group 5), 51–60 years (group 6), and 61–87 years (group 7). In our previous publications statistical significant age-dependent changes were found and a good agreement between our results and the medians of reported means, after assessment, for some age groups was shown [19-21, 24-32]. From results in Table **1** we can conclude that Zn concentration in prostate tissue increases with age, particularly after 35 years, and at about the age of 50 it is nearly 2.5 times higher than in prostate glands of males 25 years of age. Virtually the same trend can be seen for the relative volume of prostatic fluid, which equals the relative volume of the glandular lumina.

AGE-RELATED ZN CONCENTRATION CHANGES IN PERIPHERAL ZONE PROSTATE CELLS

There are few publications on Zn concentration in prostatic fluid [48-52]. Median of reported means of these concentrations agrees well with our finding [38]. It is well established that Zn concentration in prostatic fluids is independent of age [38, 48-50]. Next, relevant prostatic fluid characteristics have been taken from the literature and used in our subsequent calculations. The mean Zn concentration in prostatic fluid equals 590 mg/dm^3 and does not vary with age. From this value of the Zn concentration in prostatic fluid and values of relative prostatic fluid volume (L) (Table **1**) we can calculate the Zn content of prostatic fluid in 1 dm^3 of wet prostatic tissue (Zn^L) for different age groups, as

$$Zn^L \text{ mg} = 590 \text{ mg/dm}^3 \cdot L \cdot \text{dm}^3,$$

where L is the relative volume of the prostatic glandular lumina. If the prostate's peripheral zone is divided into two compartments comprising (a) fluid (L) and (b) solid tissue, or stromal and epithelial cells taken together, (S+E), then for these the relative volumes of (a) and (b) we can calculate the Zn content of prostatic cells in 1 dm^3 of wet peripheral zone prostatic tissue (Zn^{S+E}) for different age groups, as

$$Zn^{S+E} \text{ mg} = Zn^T \text{ mg} - Zn^L \text{ mg},$$

where Zn^T is the Zn content of 1 dm^3 of wet prostatic tissue, because T the relative volume of the prostatic tissue equals 1 and T= S+E+L. Table **2** presents results of these calculations.

Before the next step of the calculation it is necessary to accept two alternative boundary conditions: Case 1 – Zn is uniformly distributed in all cells of prostate tissue (stromal and epithelial cells), or Case 2 – Zn is contained only in epithelial cells. Using data in Table **2** for Case 1 we can calculate the intracellular Zn concentration for different age groups as

$$Zn^{\text{All cells}} \text{ mg/dm}^3 = Zn^{S+E} \text{ mg} / [(S+E) \cdot \text{dm}^3],$$

and for Case 2 as

$$Zn^{\text{Epithelial cells}} \text{ mg/dm}^3 = Zn^{S+E} \text{ mg/} (E \cdot \text{dm}^3).$$

Figure **1** depicts an age-dependence of intracellular Zn concentration for Case 1 and 2. In Case 1 the level of intracellular Zn concentration very slowly increases in the age range from newborns to 30 years. In the age range from 18 to 30 years it is virtually constant and equals about 15 mg/dm^3. A marked increase in the

Table 2: Mean values of Zn contents in all prostatic cells of peripheral zones, contained in 1 dm^3 of wet prostatic tissue for the different age groups

Group No	Mean age years	Zn^T mg	L dm^3	E dm^3	S+E dm^3	Zn^L mg	Zn^{S+E} mg
Group 1	3.3	32.6	0.045	0.203	0.955	26.6	6.00
Group 2	18.2	91.0	0.131	0.389	0.869	77.3	13.7
Group 3	26.4	105	0.156	0.384	0.844	92.0	13.0
Group 4	35.8	127	0.168	0.320	0.832	99.1	27.9
Group 5	45.4	250	0.227	0.323	0.773	134	116
Group 6	55.6	216	0.205	0.267	0.795	121	95
Group 7	68.8	189	0.136	0.256	0.864	80.2	109

Zn^T – Zn content in 1 dm^3 of wet prostatic tissue; L – volume fraction of lumen (prostatic fluid) in 1 dm^3 of wet prostatic tissue; S – volume fraction of stroma (stromal cells) in 1 dm^3 of wet prostatic tissue; E – volume fraction of epithelium (epithelium cells) in 1 dm^3 of wet prostatic tissue; (S+E) – volume fraction both of stromal and epithelium cells taken together in 1 dm^3 of wet prostatic tissue; Zn^L – Zn of prostatic fluid in 1 dm^3 of wet prostatic tissue; Zn^{S+E} – Zn of all prostatic cells in 1 dm^3 of wet prostatic tissue.

intracellular Zn level begins around age 35 years and reaches a maximum at about the age of 45 years. This maximum approximately equals 150 mg/dm^3 and is 10-fold higher than in prostate glands of males aged 18 to 30 years. After the age of 45 years intracellular Zn concentration is maintained in the range 120-150 mg/dm^3. In Case 2 the level of intracellular Zn concentration very slowly increases in the age range from newborns to 30 years and in males aged 18 to 30 years it is stable and equals about 35 mg/dm^3. A marked increase of the intracellular Zn level begins after 35 years and continues up to 70 years. Males 70 years of age have the intracellular Zn level in their epithelial cells about 430 mg/dm^3. This level is 12 times higher than in the prostate glands of males 18 to 30 years of age.

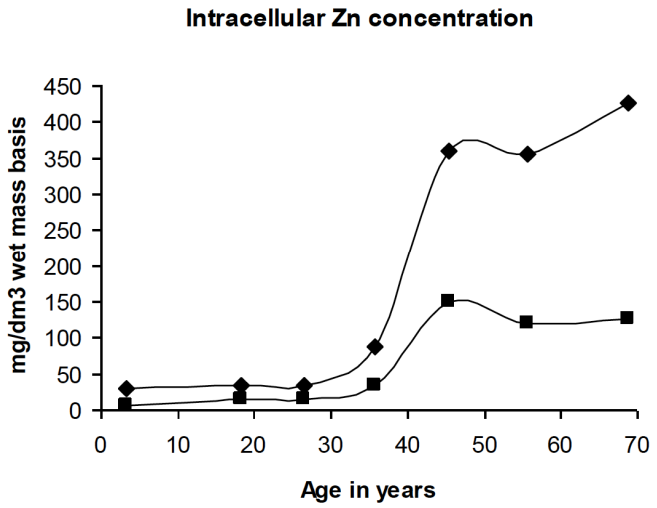

Figure 1: Age dependence of intracellular Zn concentration (mg/dm^3, wet mass basis) in the peripheral zones of the prostate.

Case 1. (■) intracellular Zn concentration in the prostate, presuming there is uniform distribution of Zn in both stromal and epithelial cells.

Case 2. (♦) intracellular Zn concentration in epithelial cells, presuming there is an accumulation of Zn only in the epithelial cells.

Despite long-term studies of Zn metabolism, its specific role in prostate function remains uncertain and reasons for the accumulation of the element in the gland are unknown. There is the well established hypothesis that a main function of prostatic epithelial cells is a production of citrates. The normal epithelial cells selectively accumulate Zn, because Zn acts as an inhibitor of an enzyme (m-aconitase), and high level of intracellular Zn arrest the Krebs cycle at the step of citrate oxidation [53]. Besides that, specialized Zn uptake transporters in prostate epithelial cells were found [54]. However, Zn was detected not only in prostatic glandular epithelium but also in the cells of stromal component [55]. Thus, the observed changes in the prostatic intracellular Zn concentration at different ages lie somewhere between Case 1 and Case 2, but in any case there is an increase of about one magnitude in intracellular Zn, starting after the age of 30 years.

Another important finding of this study is the levels of intracellular Zn concentration in the age range from 18 to 30 years. On average the intracellular Zn concentrations in prostate glands of males younger than 30 years do not increase beyond the range 15-30 mg/dm^3. This level of Zn concentration in the prostate cells is similar to mean values of this element's content in all other soft tissues or organs of the human body, including skeletal muscle (35-70 mg/dm^3), liver (30-60 mg/dm^3), lung (25-100 mg/dm^3), and kidney (25-70 mg/dm^3) [56]. Since the function of the prostate gland in the age range from 18 to 30 years is presumably normal, we must conclude that there is no accumulation of Zn by epithelial cells of the prostate which differs markedly from accumulation levels in cells of other human organs and tissues. It seems that in normal conditions prostatic epithelial cells absorb Zn, utilize this element, and then secrete it together with the prostatic fluid into the glandular lumen. It is there that the Zn accumulates. In normal conditions (in the age range 18-30 years) the rate of Zn absorption equals that of Zn transmission out of the cells and so the intracellular Zn level is maintained in the stable range 15-30 mg/dm^3. This range of intracellular Zn concentration is normal for all other cells of human body. After the age of 35 years the situation for Zn metabolism changes markedly and results in the differences of prostatic Zn levels described above The previous equilibrium between Zn absorption and transmission is no longer maintained, so Zn begins to accumulate within cells.

The intracellular Zn levels in prostate glands at age over 45 years are between 150-430 mg/dm^3 or 10-fold higher than in men aged 18 to 30 years. Excessive intracellular Zn concentrations may be harmful to normal metabolism of cells [57]. By now much data has been obtained related both to the direct and indirect action of intracellular Zn on the DNA polymeric organisation, replication and lesions, and to its vital role for cell division [58-60]. Moreover, it is known that Zn is an inhibitor of the Ca-dependent apoptotic endonuclease, which takes part in the internucleosomal fragmentation of DNA. Consequently there is a reduction of cell apoptosis [61]. Other actions of Zn

have been described. They include its action as a potent anti-apoptotic agent [62-65]. All these facts imply that age-related excessive intracellular Zn concentrations are probably one of the main factors in etiology of PCa.

When PCa was first described in 1853 it was called “a very rare disease” [66]. From that time lifespan has become much longer, diets and living conditions have changed greatly within the last two centuries or so. Evolution has not been able to “catch up” with these important changes and so these significantly different situations have probably contributed to the relatively large increase in PCa during this time, which is an infinitesimal interval on the scale of human existence. The counter argument that the high levels of intracellular Zn are coincidental to the massive rise in PCa prevalence is less likely, for there is no clear associative mechanism with the other risk factors mentioned.

CONCLUSIONS

PCa is a multietiological and multifactorial complex disease. However, from results of our measurements and calculations we see there is strong evidence for the prostatic intracellular Zn concentrations to be one of the main factors in the etiology of this malignancy. The values of the Zn concentrations in prostatic cells increase with age. By ages over 45 years the prostatic Zn levels described above are 10-fold higher than in men aged 18 to 30 years. It is well known that excessive accumulation of Zn may disturb the cell functions and may result in cellular degeneration, death or malignant transformation. In addition our hypothesis gives a possible answer to questions about the age-dependence of PCa prevalence, the location of malignant tumours (mainly in the peripheral zone of the prostate gland), and also the association of high red meat intake with an elevation in risk of PCa. All these observations and results of calculations support the hypothesis that the great increase of Zn concentrations in cells of the prostate gland with age plays a most important role in the etiology of PCa.

REFERENCES

[1] Forootan SS, Hussain S, Aachi V, Foster CS, Ke Y. Molecular mechanisms involved in the transition of prostate cancer cells from androgen dependant to castration resistant state. J Androl Gynaecol 2014; 2(2).

[2] Tao ZQ, Shi AM, Wang KX, Zhang WD. Epidemiology of prostate cancer: current status. Eur Rev Med Pharmacol Sci 2015; 19(5): 805-12.

[3] Center AA, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, Bray F. International variation in prostate cancer incidence and mortality rates. Eur Urol 2012; 61: 1079-92. http://dx.doi.org/10.1016/j.eururo.2012.02.054

[4] Cohen LA. Nutrition and prostate cancer: a review. Ann NY Acad Sci 2002; 963: 148-55. http://dx.doi.org/10.1111/j.1749-6632.2002.tb04106.x

[5] Jones BA, Liu W-L, Araujo AB, Kasl SV, Silvera SN, Soler-Vilar' H, Curnen MGM, Dubrow R. Explaining the race difference in prostate cancer stage at diagnosis. Cancer Epidemiol Biomarkers Prev 2008; 17: 2825-34. http://dx.doi.org/10.1158/1055-9965.EPI-08-0203

[6] Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun M J. Cancer statistics, 2003. CA Cancer J Clin 2003; 53: 5-26. http://dx.doi.org/10.3322/canjclin.53.1.5

[7] Rebbeck TR. Conquering cancer disparities: new opportunities for cancer epidemiology, biomarker, and prevention research. Cancer Epidemiol Biomarkers Prev 2006; 15: 1569-71. http://dx.doi.org/10.1158/1055-9965.EPI-06-0613

[8] Strahan RW. Carcinoma of the prostate: Incidence, origin, pathology. J Urol (Baltimore) 1963; 89(6): 875-80.

[9] McNeal JE, Redwine EA, Freiha FS, Stamey TA. Zonal distribution of prostatic adenocarcinoma. Am J Surg Pathol 1988; 12: 897-906. http://dx.doi.org/10.1097/00000478-198812000-00001

[10] Giovanucci E, Ascherio A, Rimm E, Stampfer M J, Colditz G A. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 1995; 87: 1767-76. http://dx.doi.org/10.1093/jnci/87.23.1767

[11] Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willet WC, Giovannucci E. A prospective study on intake of animal products and risk of prostate cancer. Cancer Causes Control 2001; 12(6): 557-67. http://dx.doi.org/10.1023/A:1011256201044

[12] Cross AJ, Peters U, Kirsh VA, Andriole GL, Reding D, Hayes RB, Sinha R. A prospective study of meat and meat mutagens and prostate cancer risk. Cancer Res 2005; 65(24): 11779-84. http://dx.doi.org/10.1158/0008-5472.CAN-05-2191

[13] Walker M, Aronson KJ, King W, Wilson JW, Fan W, Heaton JP, MacNeily A, Nickel JC, Morales A. Dietary patterns and risk of prostate cancer in Ontario, Canada. Int J Cancer 2005; 116(4): 592-98. http://dx.doi.org/10.1002/ijc.21112

[14] Stacewicz-Sapuntzakis M, Bowen PE, Borthakur G, Burns JL, Bowen PE. Correlations of dietary patterns with prostate health. Mol Nutr Food Res 2008; 52(1): 114-30. http://dx.doi.org/10.1002/mnfr.200600296

[15] Bertrand G, Vladesco R. Intervention probable du zinc dans les phenomenes de fecundation chez les animaux vertebres. Compt Rend Acad Sci (Paris) 1921; 173: 176-80.

[16] Zaichick V, Sviridova T, Zaichick S. Zinc in human prostate gland: normal, hyperplastic and cancerous. Int Urol Nephrol 1997; 29(5): 565-74. http://dx.doi.org/10.1007/BF02552202

[17] Zaichick V, Zaichick S. Role of zinc in prostate cancerogenesis. In: Mengen und Spurenelemente. 19. Arbeitstagung. Jena: Friedrich-Schiller-Universitat; 1999. pp.104-15.

[18] Zaichick V. INAA and EDXRF applications in the age dynamics assessment of Zn content and distribution in the normal human prostate. J Radioanal Nucl Chem 2004; 262: 229-34. http://dx.doi.org/10.1023/B:JRNC.0000040879.45030.4f

[19] Zaichick V, Zaichick S. 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 2013, 298(3): 1559-66. http://dx.doi.org/10.1007/s10967-013-2554-3

[20] Zaichick V, Zaichick S. 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 2013; 156(1): 357-66. http://dx.doi.org/10.1007/s12011-013-9826-1

[21] Zaichick V, Zaichick S. 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 2013; 4: 696-706. http://dx.doi.org/10.4236/ajac.2013.412084

[22] Hienzsch E, Schneider H-J, Anke M. Vergleichende Untersuchungen zum Mengen- und Spurenelementgehalt der normalen Prostata, des Prostataadenoms und des Prostatakarzinoms. Z Urol Nephrol 1970; 63: 543-46.

[23] Leissner KM, Fielkegard B, Tisell LE. Concentration and content of zinc in human prostate. Invest Urol 1980; 18: 32-5.

[24] Zaichick S, Zaichick V. Method and portable facility for energy-dispersive X-ray fluorescent analysis of zinc content in needle-biopsy specimens of prostate. X-Ray Spectrom 2010; 39: 83-9. http://dx.doi.org/10.1002/xrs.1233

[25] Zaichick S, Zaichick V. The Br, Fe, Rb, Sr, and Zn contents and interrelation in intact and morphologic normal prostate tissue of adult men investigated by energy-dispersive X-ray fluorescent analysis. X-Ray Spectrom 2011; 40(6): 464-69. http://dx.doi.org/10.1002/xrs.1370

[26] Zaichick S, Zaichick V. 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 2011; 69(6): 827-33. http://dx.doi.org/10.1016/j.apradiso.2011.02.010

[27] Zaichick V, Nosenko S, Moskvina I. 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 2012; 147(1-3): 49-58. http://dx.doi.org/10.1007/s12011-011-9294-4

[28] Zaichick S, Zaichick V, Nosenko S, Moskvina I. 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 2012; 49(2): 171-83. http://dx.doi.org/10.1007/s12011-012-9427-4

[29] Zaichick V, Zaichick S. INAA application in the assessment of chemical element mass fractions in adult and geriatric prostate glands. Appl Radiat Isot 2014; 90: 62-73. http://dx.doi.org/10.1016/j.apradiso.2014.03.010

[30] Zaichick V, Zaichick S. Determination of trace elements in adults and geriatric prostate combining neutron activation with inductively coupled plasma atomic emission spectrometry. Open Journal of Biochemistry 2014; 1(2): 16-33.

[31] Zaichick V, Zaichick S. Use of INAA and ICP-MS for the assessment of trace element mass fractions in adult and geriatric prostate. J Radioanal Nucl Chem 2014; 301(2): 383-97. http://dx.doi.org/10.1007/s10967-014-3173-3

[32] Zaichick V. 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 2015; 168(1): 44-60. http://dx.doi.org/10.1007/s12011-015-0342-3

[33] Kerr WK, Keresteci AG, Mayon H. The distribution of zinc within the human prostate. Cancer 1960; 13(3): 550-54. http://dx.doi.org/10.1002/1097-0142(196005/06)13:3<550::AID-CNCR2820130320>3.0.CO;2-X

[34] Györkey F, Min K-W, Huff JA, Györkey P. Zinc and magnesium in human prostate gland: Normal, hyperplastic, and neoplastic. Cancer Res 1967; 27, Part 1(8):1349-53.

[35] Tisell LE, Fjelkegard B, Leissner KH. Zinc concentration and content of the dorsal, lateral and medial prostatic lobes and of periurethral adenomas in man. J Urol 1982; 128(2): 403-5.

[36] Zaichick V, Tsyb A, Matveenko E, Chernichenko I. Instrumental neutron activation analysis of essential and toxic elements in the child and adolescent diets in the Chernobyl disaster territories of the Kaluga Region. Sci Total Environ 1996; 192(3): 269-74. http://dx.doi.org/10.1016/S0048-9697(96)05321-1

[37] Deering RE, Choongkittaworn M, Bigler SA, Aramburu E, King J, Brawer MK. Morphometric quantitation of stroma in human benign prostatic hyperplasia. Urology 1994; 44: 64-7. http://dx.doi.org/10.1016/S0090-4295(94)80011-1

[38] Zaichick V, Sviridova T, Zaichick S. Zinc concentration in human prostatic fluid: normal, chronic prostatitis, adenoma and cancer. Int Urol Nephrol 1996; 28(5): 687-94. http://dx.doi.org/10.1007/BF02552165

[39] Zaichick S, Zaichick V. Relations of morphometric parameters to zinc content in paediatric and nonhyperplastic young adult prostate glands. Andrology 2013; 1(1): 139-46. http://dx.doi.org/10.1111/j.2047-2927.2012.00005.x

[40] Zaichick V, Zaichick S. Relations of bromine, iron, rubidium, strontium, and zinc content to morphometric parameters in pediatric and nonhyperplastic young adult prostate glands. Biol Trace Elem Res 2014; 157(3): 195-204. http://dx.doi.org/10.1007/s12011-014-9890-1

[41] Zaichick V, Zaichick S. Relations of the Al, B, Ba, Br, Ca, Cl, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr, and Zn mass fractions to morphometric parameters in pediatric and nonhyperplastic young adult prostate glands. BioMetals 2014; 27(2): 333-48. http://dx.doi.org/10.1007/s10534-014-9716-9

[42] Zaichick V, Zaichick S. The distribution of 54 trace elements including zinc in pediatric and nonhyperplastic young adult prostate gland tissues. Journal of Clinical and Laboratory Investigation Updates 2014; 2(1): 1-15. http://dx.doi.org/10.14205/2310-9556.2014.02.01.1

[43] Zaichick V, Zaichick S. Androgen-dependent chemical elements of prostate gland. Androl Gynecol: Curr Res 2014; 2(2).

[44] Zaichick V, Zaichick S. Age-related histological and zinc content changes in adult nonhyperplastic prostate glands. Age 2014; 36(1): 167-81. http://dx.doi.org/10.1007/s11357-013-9561-8

[45] Costello LC, Franklin RB. Zinc is decreased in prostate cancer: an established relationship of prostate cancer. J Biol Inorg Chem 2011; 16(1): 3-8. http://dx.doi.org/10.1007/s00775-010-0736-9

[46] Banas A, Banas K, Kwiatek WM, Gajda M, Pawlicki B, Cichocki T. Neoplastic disorders of prostate glands in the light of synchrotron radiation and multivariate statistical analysis. J Biol Inorg Chem 2011; 16(8): 1187-96. http://dx.doi.org/10.1007/s00775-011-0807-6

[47] Avtandilov GG. Morphometry in pathology, Moscow: Medicina; 1973.

[48] Mackenzie AR, Hall T, Whitmore WFJr. Zinc content of expressed human prostate fluid. Nature 1962; 193(4810): 72-3. http://dx.doi.org/10.1038/193072a0

[49] Fair WR, Cordonnier JJ. The pH of prostatic fluid: A reappraisal and therapeutic implications. J Urol 1978; 120(6): 695-98.

[50] Kavanagh JP. Zinc binding properties of human prostatic tissue, prostatic secretion and seminal fluid. J Reprod Fert 1983; 68(2): 359-63. http://dx.doi.org/10.1530/jrf.0.0680359

[51] Gómes Y, Arocha F, Espinoza F, Fernandez D, Vásquez A, Granadillo V. Niveles de zinc en líquido prostático de pacientes con patologías de próstata. Invest Clin 2007; 48(3): 287-94.

[52] Costello LC, Franklin RB. Prostatic fluid electrolyte composition for the screening of prostate cancer: a potential solution to a major problem. Prostate Cancer Prostate Dis 2009; 12(1): 17-24. http://dx.doi.org/10.1038/pcan.2008.19

[53] Costello LC, Franklin RB. Novel role of zinc in the regulation of prostate citrate metabolism and its implications in prostate cancer. Prostate 1998; 35: 285-96. http://dx.doi.org/10.1002/(SICI)1097-0045(19980601)35:4<285::AID-PROS8>3.0.CO;2-F

[54] Kolenko V, Teper E, Kutikov A, Uzzo R. Zinc and zinc transporters in prostate carcinogenesis**.** Nat Rev Urol 2013; 10: 219-26. http://dx.doi.org/10.1038/nrurol.2013.43

[55] Ide-Ektessabi A, Fujisawa F, Sugiruma K, Kitamura Y, Gotoh A. Quantitative analysis of zinc in prostate cancer tissue using synchrotron radiation microbeams. X-Ray Spectrom 2002; 31: 7-11. http://dx.doi.org/10.1002/xrs.532

[56] Iyengar GV. Reevaluation of the trace element content in reference men. Radiat Phys Chem 1998; 51: 545-60. http://dx.doi.org/10.1016/S0969-806X(97)00202-8

[57] Bozym RA, Chimienti F, Giblin LJ, Gross GW, Korichneva I, Li Y, Libert S, Maret W, Parviz M, Frederickson CJ, Thompson RB. Free zinc ions outside a narrow concentration range are toxic to a variety of cells *in vitro*. Exp Biol Med (Maywood) 2010; 235(6): 741-50. http://dx.doi.org/10.1258/ebm.2010.009258

[58] Schwartz MK. Role of trace elements in cancer. Cancer Res 1975; 35: 3481-87.

[59] Matusik RJ, Kreis C, McNicol P, Sweetland R, Mullin C, Fleming WH, Dodd JG. Regulation of prostatic genes: role of androgens and zinc in gene expression. Biochem Cell Biol 1986; 64: 601-7. http://dx.doi.org/10.1139/o86-083

[60] Blok LJ, Grossmann ME, Perry JE, Tindall DJ. Characterization of an early growth response gene, which encodes a zinc finger transcription factor, potentially involved in cell cycle regulation. Mol Endocrinol 1995; 9(11): 1610-20.

[61] Zezerov YeG. Hormonal and molecular-biological factors of prostate cancer pathogenesis. Voprosy Oncologii 2001; 47(2): 174-81.

[62] Truong-Tran AQ, Ho LH, Chai F, Zalewski PD. Cellular zinc fluxes and the regulation of apoptosis/gene-directed cell death. J Nutr 2000; 130(5S Suppl): 1459S-66S.

[63] Kontargiris E, Vadalouka A, Ragos V, Kalfakakou V. Zinc inhibits apoptosis and maintains NEP downregulation, induced by Ropivacaine, in HaCaT cells. Biol Trace Elem Res 2012; 150: 460-6. http://dx.doi.org/10.1007/s12011-012-9492-8

[64] Liang D, Yang M, Guo B, Cao J, Yang L, Guo X, Li Y, Gao Z. Zinc inhibits H_2O_2-induced MC3T3-E1 cells apoptosis via MAPK and PI3K/AKT pathways. Biol Trace Elem Res 2012; 148: 420-9. http://dx.doi.org/10.1007/s12011-012-9387-8

[65] Zhang X, Liang D, Guo B, Yang L, Wang L, Ma J. Zinc inhibits high glucose-induced apoptosis in peritoneal mesothelial cells. Biol Trace Elem Res 2012; 150: 424-32. http://dx.doi.org/10.1007/s12011-012-9473-y

[66] Denmeade SR, Isaacs JT. A history of prostate cancer treatment. Nat Rev Cancer 2002; 2(5): 389-96. http://dx.doi.org/10.1038/nrc801

Received on 04-04-2016 Accepted on 18-05-2016 Published on 10-08-2016

http://dx.doi.org/10.6000/1927-7229.2016.05.03.5