NUCLEAR ANALYTICAL METHODS IN BENIGN PROSTATIC HYPERPLASIA AND PROSTATE CANCER DIAGNOSTICS

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Postulate 2 of Medical Elementology:

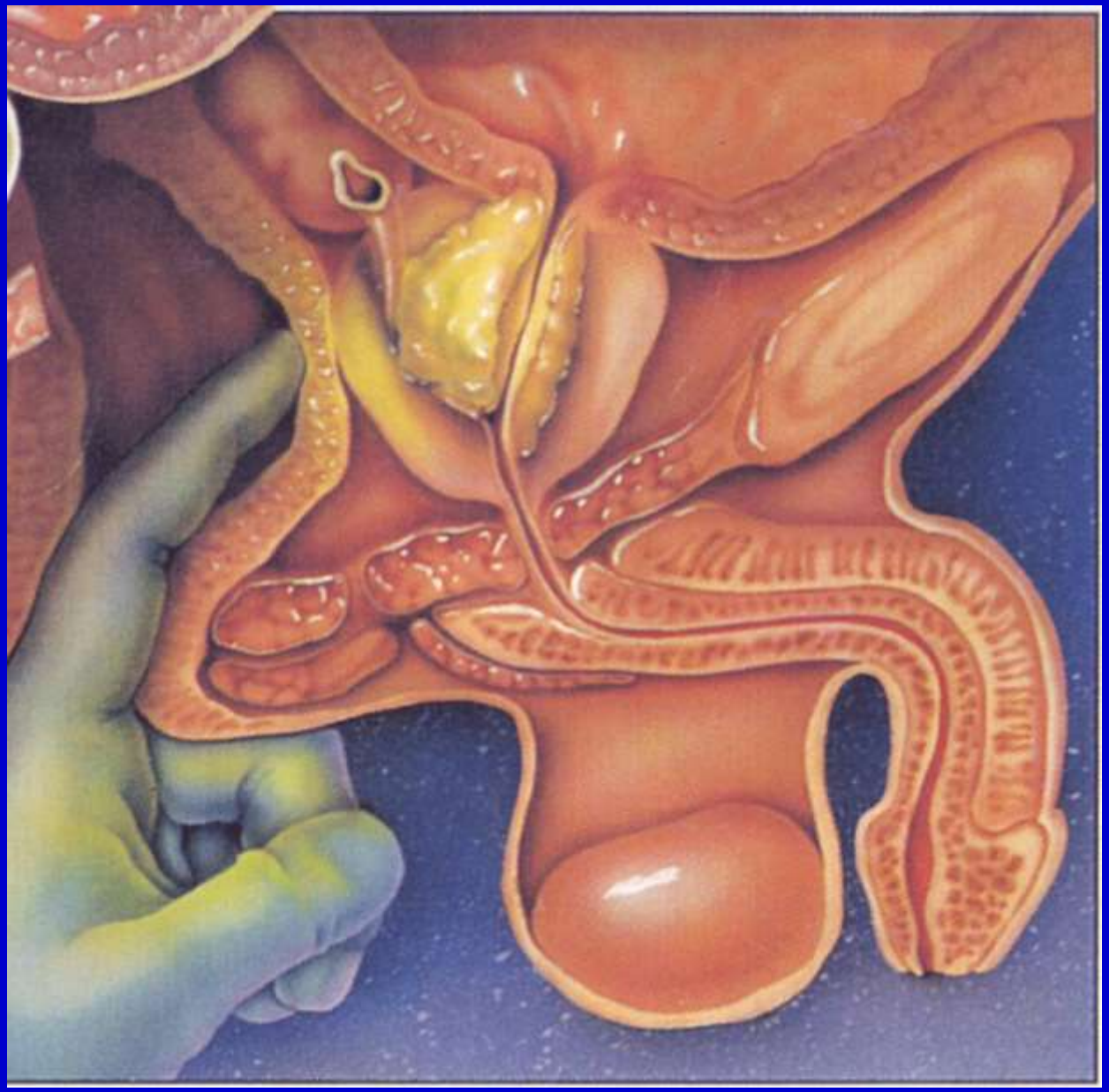
The levels and metabolic fluxes of chemical elements are controlled by homeostatic regulation (Differential homeostasis)

In all organisms differential homeostasis of chemical elements is carried out, i.e. at all levels of their organization (the internal environs, organs, tissues, cells, etc.) the content of chemical elements is maintained at certain levels. These levels can change with age and under the influence of various exogenous and endogenous factors, within, however, the certain ranges and limits. Differential homeostasis is a cause of irregularity in distribution and of difference in exchange velocity of chemical elements in organs, tissues, fluids and other structural formations of the organism.

Zaichick V., Agadjanyan N.A. Vesti Vosstan. Med., 2004, vol. 3, №9, 19-24.
Zaichick V. J. Radioanal. Nucl. Chem., 2006, Vol. 269, No. 2, 303-309.

Prostate cancer is one of prevalent cancer diseases in men of Russia. The most used method for earlier diagnosis is digital rectal examination, transrectal ultrasound examination and PSA-test. However due to high incidence of false-positive diagnoses (up to 80%) the above diagnostic methods are insufficient for reliable formation of groups under risk following screening prophylactic examinations. Use of transrectal biopsy for hystologic examination of biopsy material is problematical due to labor-intensive hystologic examination made by big team of skilled pathomorphologists. At the first visit to urologist about 60% of patients have metastases and in the first year after diagnosing about 30% of patients die, as screening prophylactic examination is not carried out in Russia. Development and use of new methods for early diagnosis of prostate cancer acceptable for screening examination remains the problem of great concern.

Prostate Gland



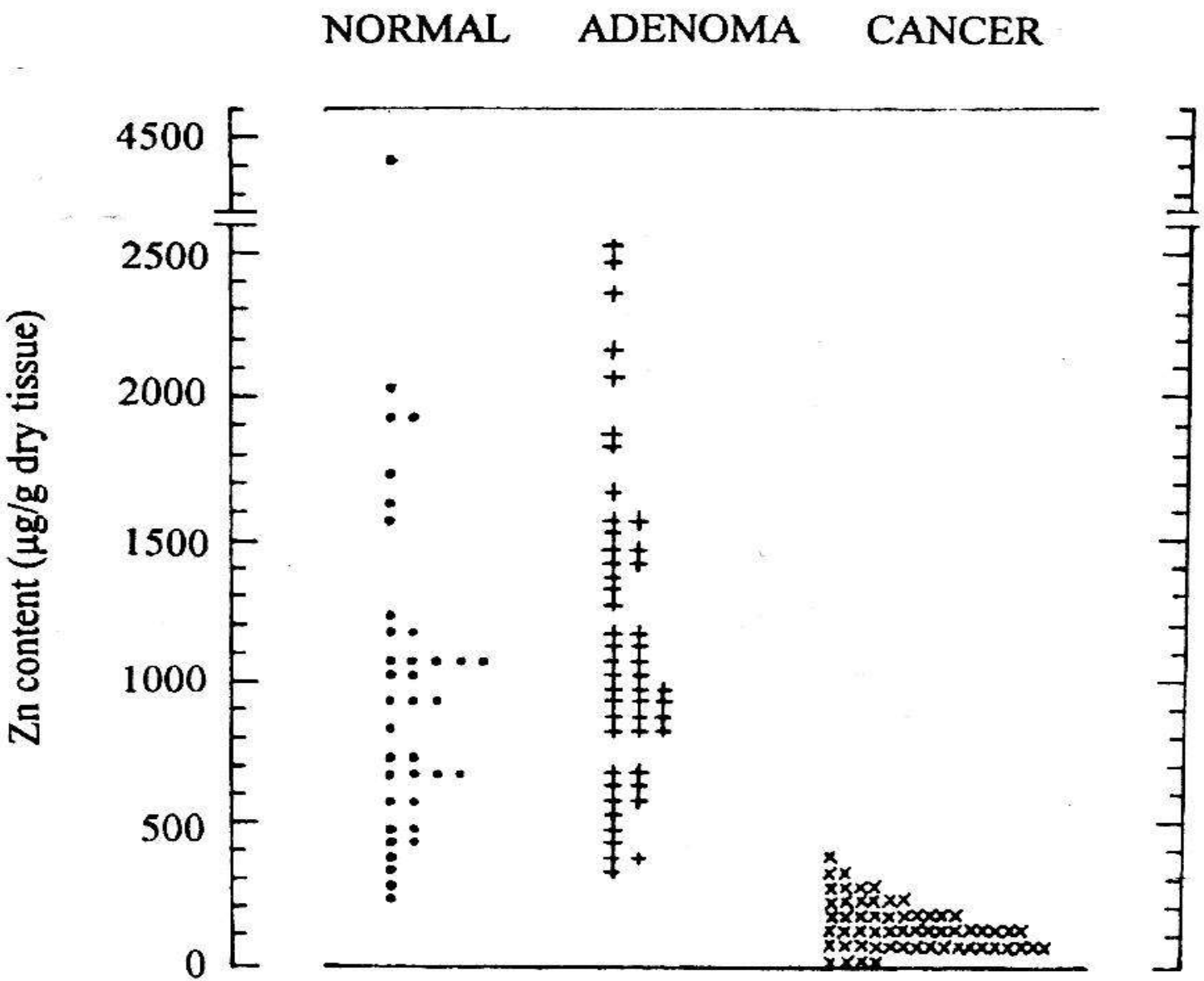
1.Differential diagnostics of cancer and benign hyperplasia of the prostate gland using level of Zn content in biopsy

To analyze materials of transrectal puncture tissue biopsy and resected materials zinc content was estimated for benign prostate hyperplasia (BPH) and cancer (PCa). There were 109 patients studied (50 BPH and 59 cancer). Control group consisted of 37 intact glands of men died an unexpected death (accident, murder, acute cardiac insufficiency, etc.). All materials studied were divided into two parts. One of them was morphologically examined while zinc content of another one was estimated.

Table 1.1. **Zinc mass fraction in prostate tissues (μg/g dry tissue)**

	Normal (n = 37)	Hyperplastic (n = 50)	Cancerous (n = 59)
Mean	1018	1142	146
SE	±124	±77	±10
SD	±754	±543	±76
Median	910	1038	134
Mode	910	1110	87
Geometric mean	822	1019	127
Min-Max	204-4403	312-2515	27-385

Fig. 1.1. Zn mass fraction in normal prostate, BPH and cancer



Our data made it possible to estimate adequately the diagnostic importance of using information about zinc content for differential diagnostics of BPH and cancer. If zinc level of 350 μg/g (M + 3SD) dry tissue was assumed to be a limit value of these two diseases (*Fig.4.1*), the results of estimation are the following:

$$\text{Sensitivity} = \frac{\text{(correct positive test – (CPT))}}{\text{(CPT+ false-negative test (FNT))}} \times 100\% = 98 \pm 2\%$$

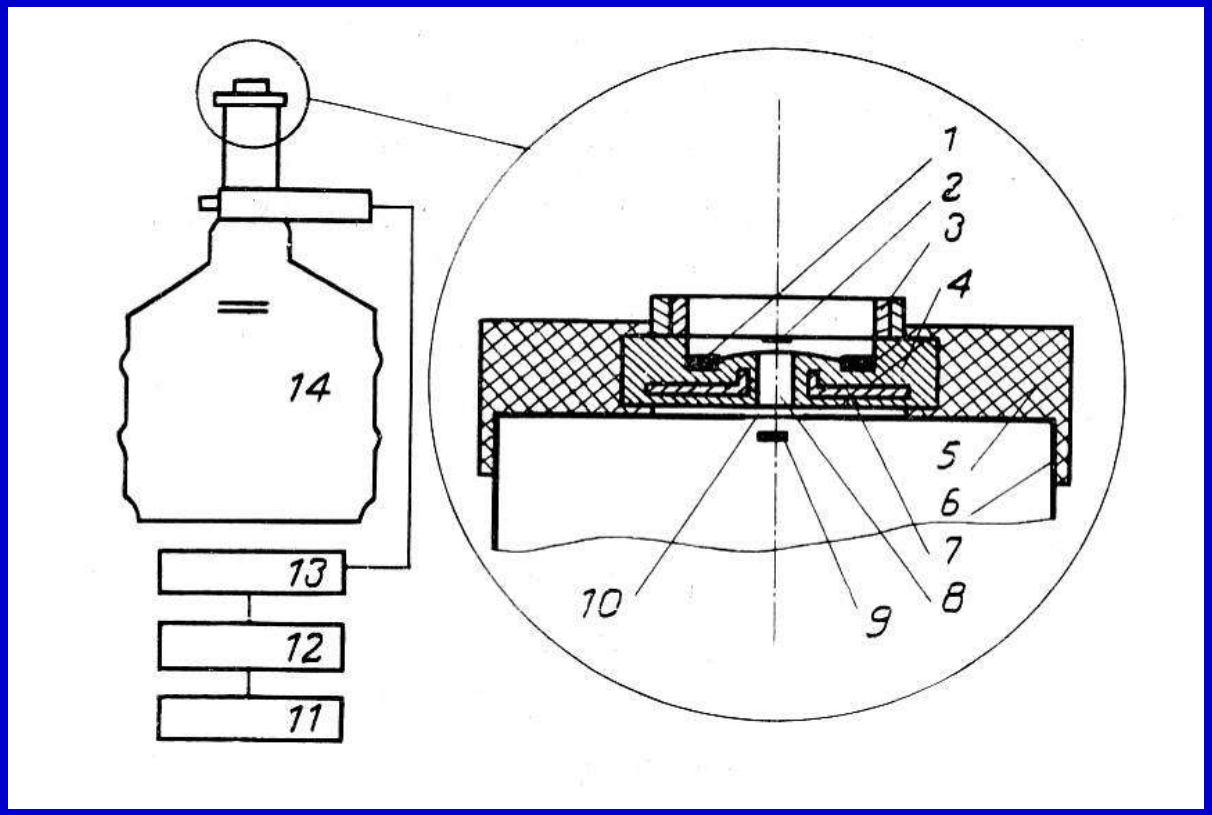
$$\text{Specificity} = \frac{\text{(correct negative test (CNT))}}{\text{(CNT+ false-positive test (FPT))}} \times 100\% = 98 \pm 2\%$$

$$\text{Accuracy} = \frac{\text{CPT+CNT}}{\text{CPT+FNT+CNT+FPT}} \times 100\% = 98 \pm 2\%$$

The method was covered by author's certificate on innovation and published in international journals.

Zaichick et al. Author's certificate № 764660, 27.10.1977.
Zaichick et al. J. Radioanal. Nucl. Chem., 1997, Vol. 217, No 2, pp. 157-161.
Zaichick et al. Int. Urol. Nephrol., 1997, Vol. 29, No 5, pp. 565-574.
Zaichick et al. Applied Radiation and Isotopes, 2012, Vol. 70, 81-87

Fig. 1.2. Scheme of facility for EDXRF measurement of Zn content in samples of prostate tissue including puncture biopsy specimens



1 - annular ^{109}Cd source
2 - biopsy specimen (tissue sample, standard) on 4 μm dacron backing
3 - thin-walled plastic cylinder for holding biopsy specimens, tissue samples and standards in the measurement position
4 – pure aluminum A-000
5 – plastic holder
6 - detector cryostat wall
7 – shield made of Ta
8- 5mm or 10 mm separable collimator
9 - Si(Li)-detector crystal
10 - detector beryllium «window»
11 – printer or PC
12 – MCA
13 – spectrometric unit
14 – liquid nitrogen in a Dewar vessel

Fig. 1.3. **Photo of facility for EDXRF measurement of Zn content in samples of prostate tissue including puncture biopsy material**

СОЮЗ СОВЕТСКИХ СОЦИАЛИСТИЧЕСКИХ РЕСПУБЛИК

ГОСУДАРСТВЕННЫЙ КОМИТЕТ СССР
ПО ДЕЛАМ ИЗОБРЕТЕНИЙ И ОТКРЫТИЙ

АВТОРСКОЕ СВИДЕТЕЛЬСТВО

№ 764660

На основании полномочий, предоставленных Правительством СССР, Государственный комитет СССР по делам изобретений и открытий выдал настоящее авторское свидетельство на изобретение:

"Способ дифференциальной диагностики злокачественных и доброкачественных опухолей предстательной железы"

Автор (авторы): Дунчик Василий Николаевич, Жербин Евгений Александрович, Зайчик Владимир Ефимович, Леснов Анатолий Ильич и Свирадова Татьяна Владимировна

Заявитель: НАУЧНО-ИССЛЕДОВАТЕЛЬСКИЙ ИНСТИТУТ МЕДИЦИНСКОЙ РАДИОЛОГИИ АМН СССР

Заявка № 2537192 Приоритет изобретения 27октября 1977г.

Зарегистрировано в Государственном реестре изобретений СССР

28 мая 1980г.

Действие авторского свидетельства распространяется на всю территорию Союза ССР.

Председатель Комитета

Начальник отдела

МПФ Головка. 1979. Зак. 79-3083.

The method was covered by author's certificate on innovation (*Author's certificate № 764660)*

Subject:

Method of differential diagnostics of benign and malignant tumor of prostate

Author:

Zaichick et al.

Date:

27 October 1977

Weizmann Institute of Science, Sheba and Kaplan Medical Centers

Shilstein S.Sh. et al. Prostatic Zn determination for prostate cancer diagnosis. Talanta, 2006, 70, 914-921

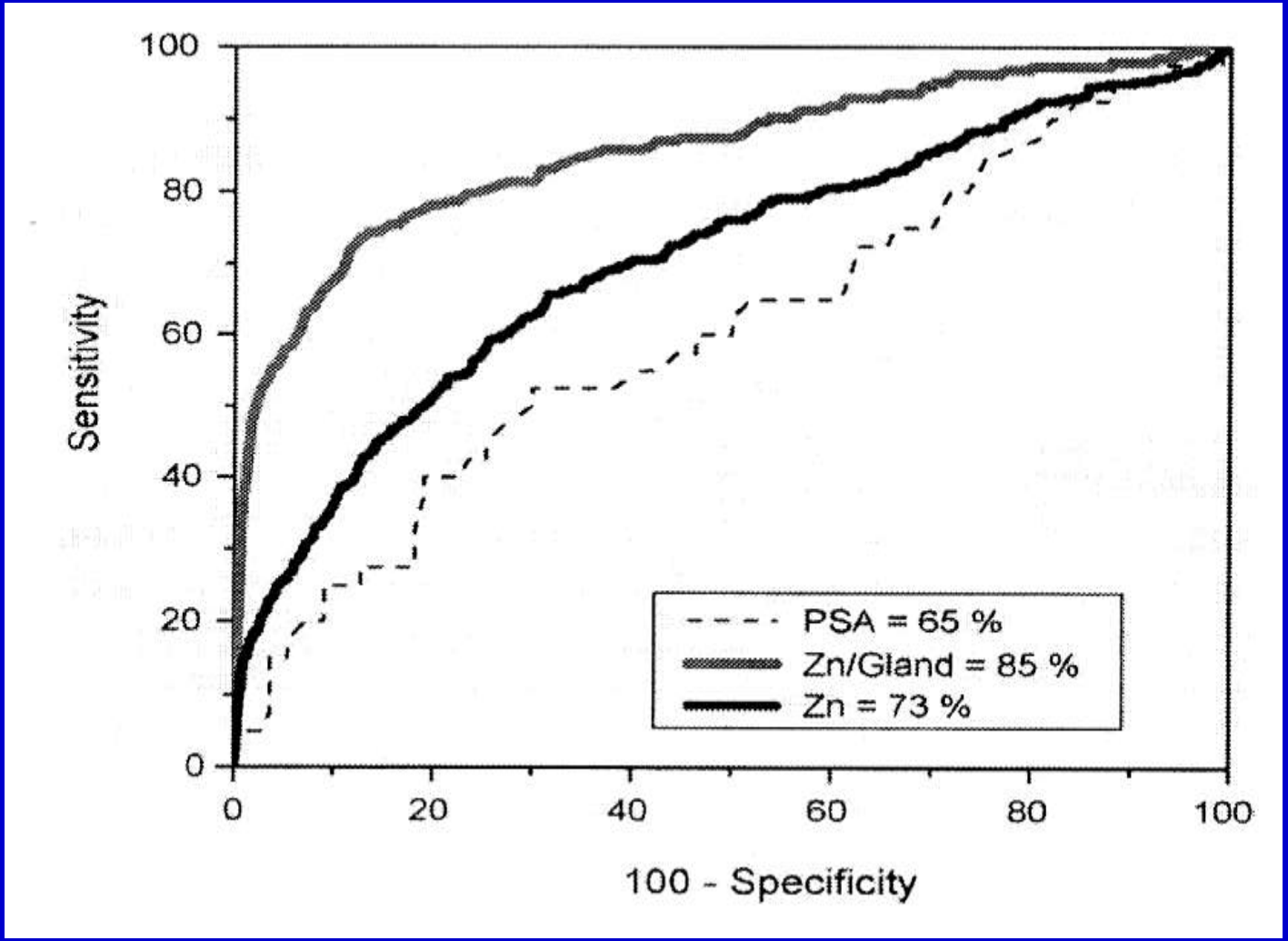


Fig. 1.4. Curves of sensitivity vs. specificity for PSA, Zn (SMP) and Zn normalized to % glands (single measurement points). An ideal diagnostic tool will have 100% sensitivity and 100% specificity, namely a step function with area 100%

2. Differential diagnostics of prostate cancer and benign prostatic hyperplasia by *in vivo* EDXRF of zinc content in prostate tissues

Test of prostate tissue without visible lesions taken from operation materials of prostate cancer and benign prostatic hyperplasia demonstrated that zinc level was close to the norm. This finding allowed us to offer ratio **"zinc in lesion / zinc in non-lesional tissue"** for diagnostic purposes. The use of this ratio opened the possibilities of the development of the method for *in vivo* differential diagnostics of prostate cancer and benign prostatic hyperplasia where Zn content in intact prostate tissue served as internal standard. For the *in vivo* transrectal EDXRF of Zn in prostate a device in the form of cylinder 30 mm in diameter was done in cooperation with the Institute of Earth (the University of Leningrad). Inside the device Si(Li) detector and sheathed source with ^{109}Cd were placed, windows of the source and the crystal collimators were located on the side surface of cylinder. The detector crystal was cooled by a portable electric refrigerator. Model experiments showed good results. In natural condition the resolution was poor due to rapid overheating of the detector. Further improvement of the device required reducing diameter of the device to 20 mm and maintaining proper temperature of the detector during its being in a rectum.

Weizmann Institute of Science

Shilstein S.Sh. et al. Prostatic Zn determination for prostate cancer diagnosis. Talanta, 2006, 70, 914-921

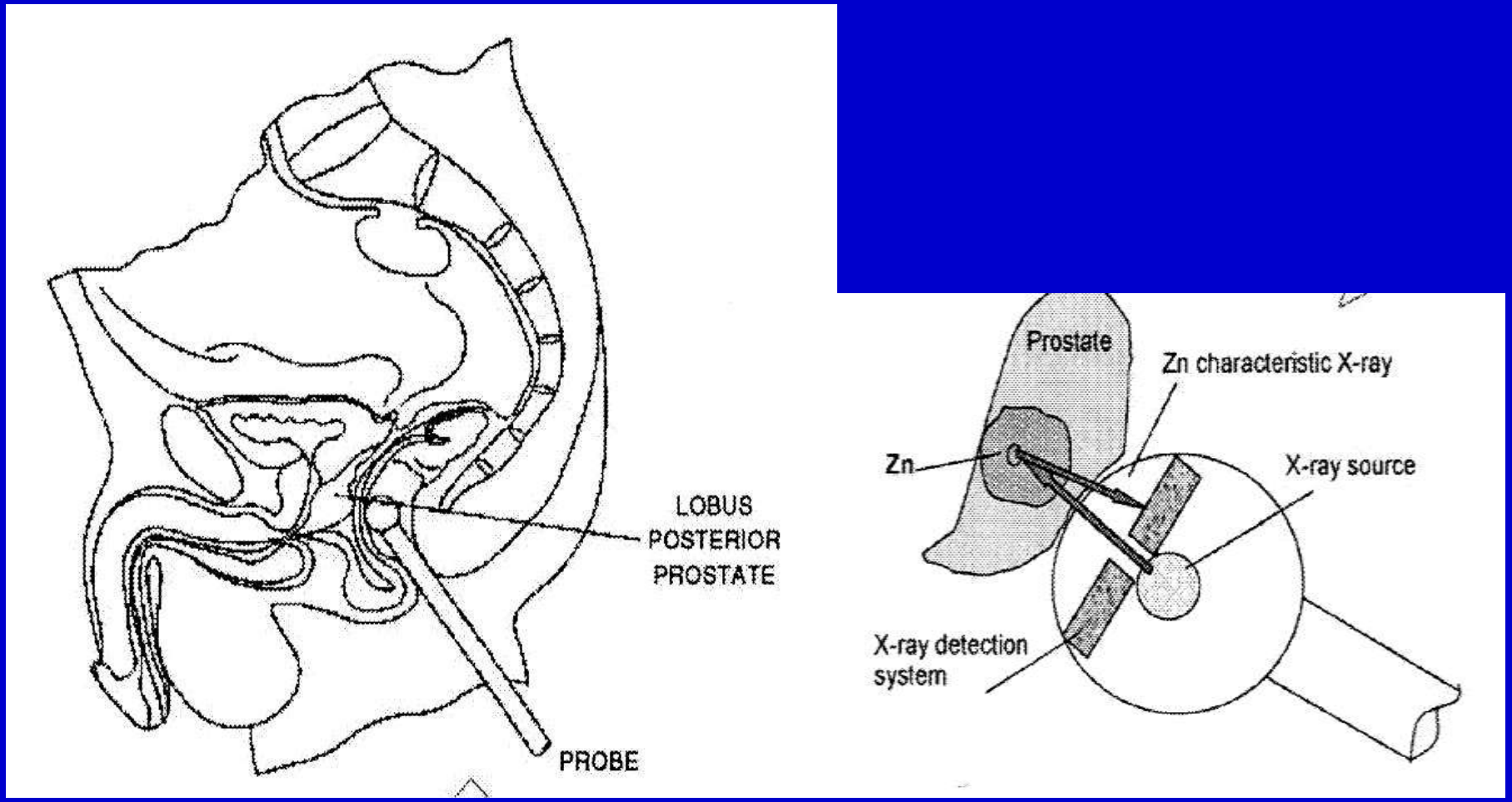


Fig. 2.1. The proposed XRF *trans*-rectal probe concept for prostate cancer diagnosis.

1. Cortesi M., Fridman E., Volkov A., Shilstein S., Chechik R., Breskin A., Vartsky D., Raviv G., Ramon J. New Prospective for Non-Invasive Detection, Grading, Size Evaluation, and Tumor Location of Prostate Cancer. Prostate 70: 1701–1708, 2010

2. International (PCT) patent application. Method and system for detecting and grading prostate cancer. World Intellectual Property Organization (WIPO), July 2009, number WO 2009/083988

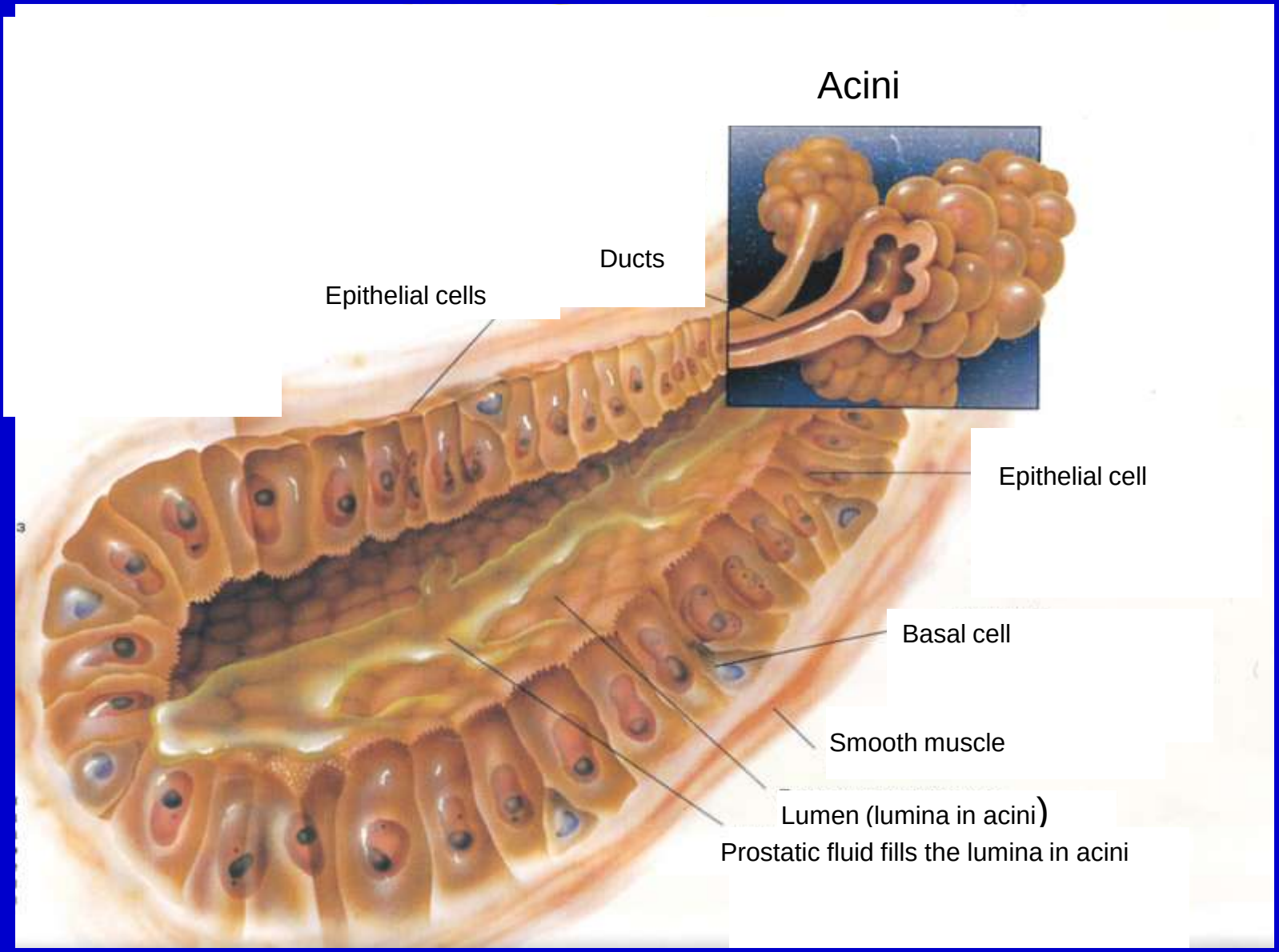
The zinc-based imaging approach combines two directions. It incorporates the natural bio-marker, intimately related to the adenocarcinoma onset and progression and strongly correlated to the cancer grade, within an imaging modality. The trans-rectal probe that will be based on this approach, is expected to provide location, extension and grading information, and could be used at various stages of the disease management.

3. Age-related histological and zinc content changes in nonhyperplastic prostate glands

It is well known that zinc levels in the human prostate are almost 10 times higher than in other soft tissues (Zaichick et al. 1997). The high content of zinc in the prostate suggests that zinc may play a role in prostate function and health. Zinc is the second most abundant metal in the human body, serving as a cofactor for more than 300 enzymes with various physiological functions (Coleman 1992). Despite the long-term study of Zn metabolism, full reasons explaining the specific role of Zn in prostate function and the total concentration of the element in the gland are still not fully understood. There is only the hypothesis that in normal prostate tissue, Zn acts as an inhibitor of an enzyme (m-aconitase), which is part of the Krebs cycle (Costello and Franklin 1998). Besides that, specialized Zn uptake transporters in prostate epithelial cells were found (Beck et al. 2004; Franklin et al. 2005; Desouki et al. 2007). However, Zn was found not only in glandular epithelium but in the stromal component too (Ide-Ektessabi et al. 2002). Thus, the long standing questions about the main pool and the local distribution of Zn in prostate tissue still remain incompletely understood (Mawson and Fischer 1952; Hoare et al. 1956; Siegal et al. 1961; Kar and Chowdhury 1968; Dhar et al. 1973; Morita 1981; Leake et al. 1983; Tvedt et al. 1989; Bataineh 2002; Franklin et al. 2005).

Zaichick V. J. Radioanal. Nucl. Chem., 2004, Vol. 262, No.1, pp. 229-234.

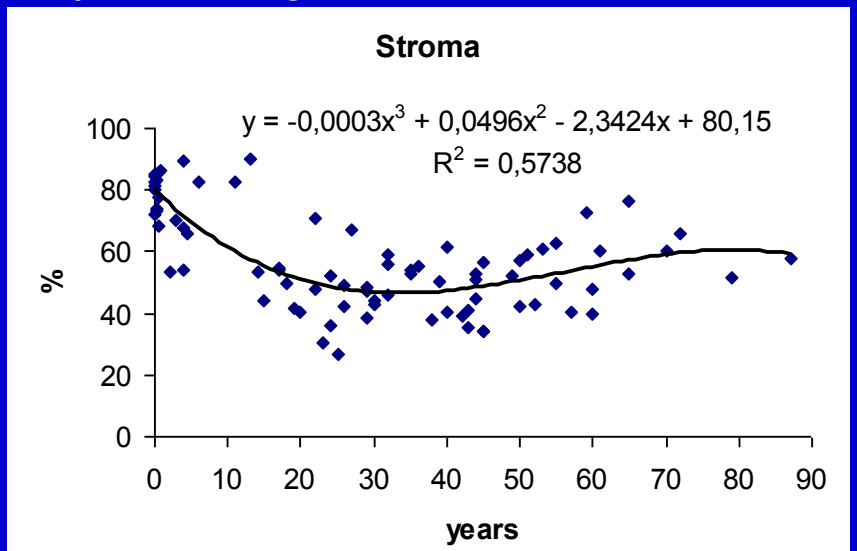
Fig. 3.1. Morphology of prostate gland

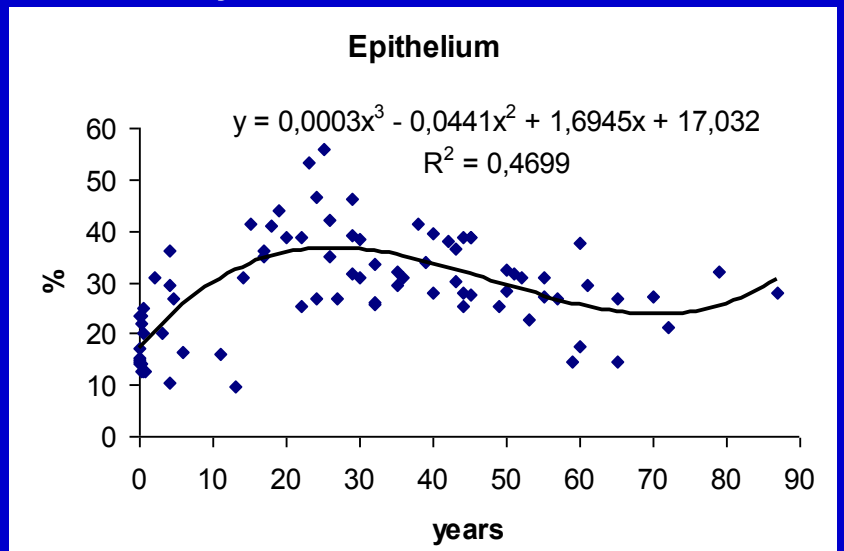


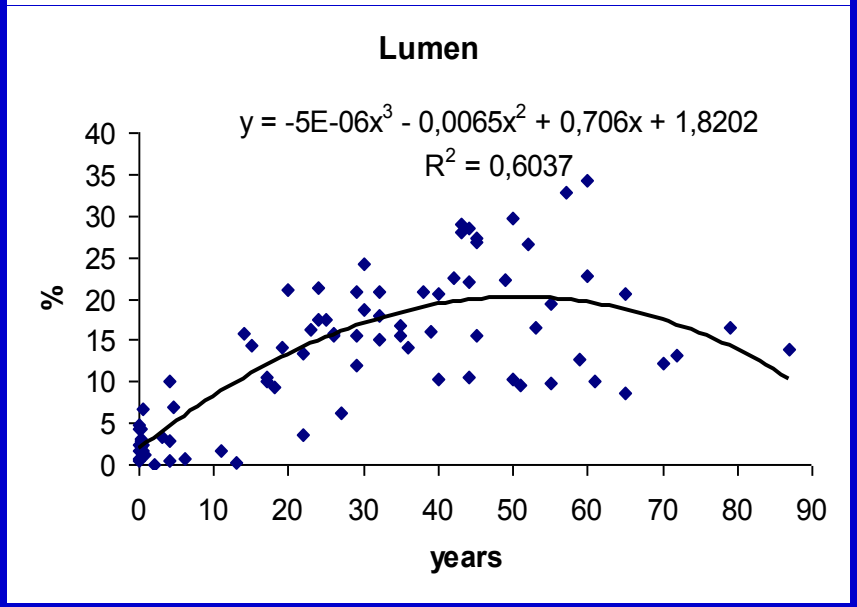
The prostatic tissue contains three main components: glandular tissue, prostatic fluid, and fibromuscular tissue or stroma. Glandular tissue includes acini and ducts. Epithelial cells (E) surround the periphery of the acini and luminal surfaces (L) in acini (glandular lumen). Prostatic fluid fills the lumina in acini (glandular lumen). Stromal tissue (S) is composed of smooth muscle, connective tissue, fibroblasts, nerves, lymphatic and blood vessels. Thus, the volume of the prostate gland may be presented as a sum of volumes (E + L + S).

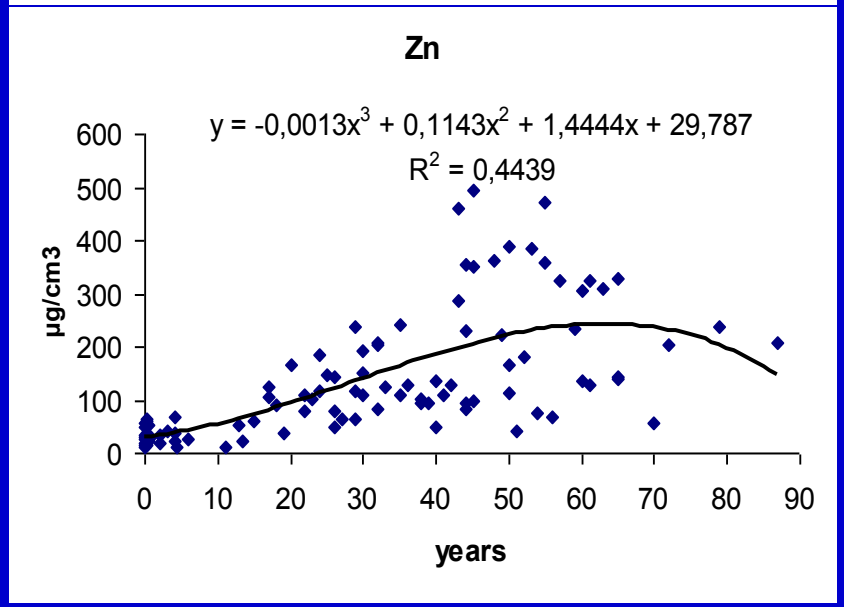
In order to clarify the age-related histological and Zn content changes in nonhyperplastic prostate glands, a quantitative morphometric and Zn content studies were performed, respectively. The prostates were obtained at autopsy from 101 subjects (European-Caucasian, aged <1–87 years) who died mainly from trauma. None of the subjects presented any clinical symptoms of prostatic disease and all prostates were classified as histologically normal. Each prostate was divided into two portions. One tissue portion was reviewed by an anatomical pathologist while another was used for the Zn mass fraction measurement. The mean percent volume of the stroma (S), glandular epithelium (E), and glandular lumen (L) were determinedfor for each prostate specimen. It was found that normal prostate tissue undergoes substantial changes during this period of life.

Fig.3.2. Individual data sets for the percent volume (stroma, epithelium, lumen, and glandular component) and zinc concentration in the nonhyperplastic prostate gland of males between ages <1–87 years and trend lines









A significant positive correlation between the prostatic Zn and percent volume of glandular lumen (r = 0.74, $p \leq 0.001$) was seen (Table 3.1, column "Σ all age groups"). This indicates that the glandular lumen is a main pool of Zn concentration in the normal human prostate. Because the volume of the glandular lumen reflects the volume of prostatic fluid, we can conclude that the Zn more tightly binds with the prostatic fluid than with glandular cells.

Table 3.1. Changes of correlations (r - coefficient of correlation) between the Zn mass fraction and morphometric parameters in nonhyperplastic prostate tissue with age

Histologic parameter	Age group (Range of years, M±SD year, number of samples)							
	I	II	III	IV	V	I+II+III	IV+V	Σ all
	<1-6	11-15	16-30	31-50	51-70	<1-30	31-70	<1-87
	1.4±1.8	13±2	24±4	41±6	59±6	12±11	49±11	31±22
	n=24	n=5	n=21	n=28	n=20	n=50	n=48	n=100
Stroma (S)	0.19	-0.26	-0.31	**-0.60**	-0.20	**-0.63**	**-0.34**	**-0.51**
Epithelium (E)	-0.10	0.41	0.04	0.03	-0.14	**0.56**	-0.09	0.19
Lumen (L)	-0.25	0.32	**0.54**	**0.81**	**0.37**	**0.68**	**0.58**	**0.74**

Statistically significant r -values are given **in bold**

4. Differential diagnostics of cancer and benign hyperplasia of the prostate gland by EDXRF of Zn content in prostatic fluid

Characteristic property of the prostate gland is accumulation of zinc, which is used in synthesis of prostatic fluid. Prostatic fluid is easy available, taking the fluid is non-traumatic procedure.

In our study the samples of expressed prostatic fluid obtained by digital rectal massage were used. 20 μL of secretion were taken with a capillary tube from every specimen to analyse zinc while the rest of the fluid was studied cytologically and bacteriologically. The chosen 20 μL of secretion were dropped to a special backing, the bottom of which was made of dacron film 4 μm thick. Then drops were dried in a vacuum. For prostatic fluid mean value of K_{dry} = 0.098. As a drop area was within 1 cm^{-2} a sample surface density does not exceed 0.00862 $g \cdot cm^{-2}$ (the criterion of “thin sample”).

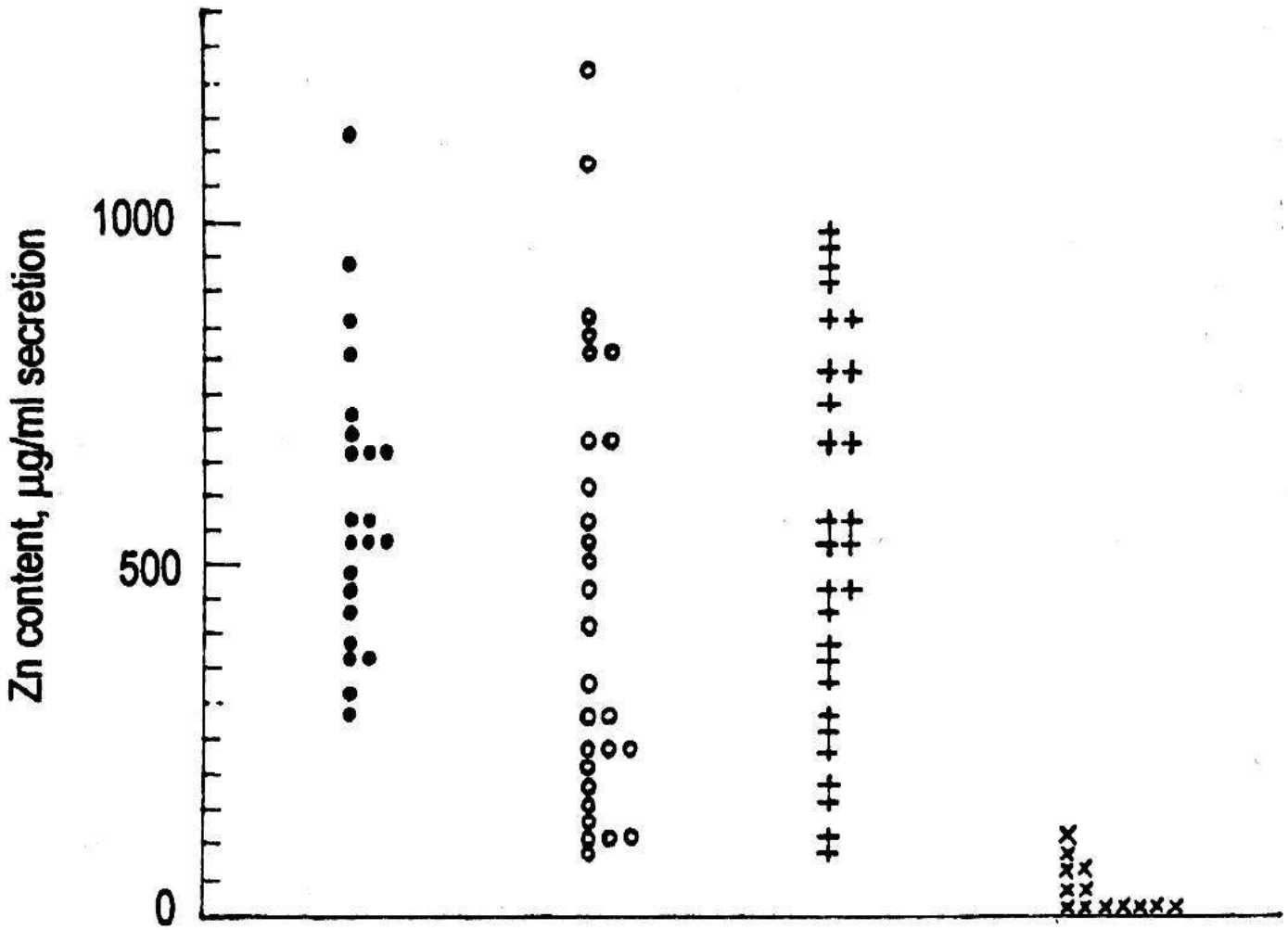
The Zn concentrations in prostatic fluid samples were measured by the EDXRF facility used for prostate biopsies investigation. For analysis zinc in prostatic fluid 10-min exposition was sufficient, uncertainty was less than 5%.

Groups of patients suffering from chronic prostatitis, BPH and PCa consisted of 28, 28 and 13 men, respectively, were examined. The control group included 22 healthy volunteers. Expressed prostatic fluid was obtained by digital rectal massage. The zinc concentration of intact prostatic fluid was 573±38 (SE) μg/mL. Almost no difference was found between the zinc concentration for chronic prostatitis and that for BPH, and those for normal levels being 455±60 (SE) and 540±50 (SE) μg/mL, respectively. PCa resulted in significant decrease of zinc secretion content averaging 34.7±9.6 μg/mL, $p<0.000001$.

Table 4.1. Zinc concentration in prostatic fluid (μg/mL)

	n	Mean	±SEM	±SD	Median	Geometric mean	Min-Max
Normal	22	573	38	177	552	556	291-941
Chronic prostatitis	28	455	60	317	370	345	76.2-1209
BPH	28	540	50	270	530	450	86.0-977
Cancer	13	34.7	9.6	34.6	21.4	17.3	2.8-101

Fig. 4.1. Zn concentration in human prostatic fluid: normal ( ), chronic prostatitis (o), benign prostatic hyperplasia (+) and malignant tumours ( )



Our data made it possible to estimate adequately the diagnostic importance of using information about zinc concentration in prostatic fluid for differential diagnostics of BPH and cancer. A 100 μg/ml secretion limit was used for the selection. The characteristics of the diagnostic method obtained were as follows:

$$\text{Sensitivity} = \frac{\text{(correct positive test – (CPT))}}{\text{(CPT+ false-negative test (FNT))}} \times 100\% = 93 \pm 8\%$$

$$\text{Specificity} = \frac{\text{(correct negative test (CNT))}}{\text{(CNT+ false-positive test (FPT))}} \times 100\% = 96 \pm 4\%$$

$$\text{Accuracy} = \frac{\text{CPT+CNT}}{\text{CPT+FNT+CNT+FPT}} \times 100\% = 95 \pm 4\%$$

The method was covered by author's certificate on innovation.

Zaichick et al., Aurthor's certificate № 997281, 30.03.1981

Zaichick et al. Int. Urol. Nephrol., 1996, Vol. 28, No 5, pp. 687-694.

СОЮЗ СОВЕТСКИХ СОЦИАЛИСТИЧЕСКИХ РЕСПУБЛИК

ГОСУДАРСТВЕННЫЙ КОМИТЕТ СССР
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№ 997281

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"Способ диагностики заболеваний предстательной железы"

Автор (авторы): Зайчик Владимир Ефимович, Ыыб Анатолий Федорович, Лунчик Василий Николаевич и Свиридова Татьяна Владимировна

Заявитель: НАУЧНО-ИССЛЕДОВАТЕЛЬСКИЙ ИНСТИТУТ МЕДИЦИНСКОЙ РАДИОЛОГИИ АМН СССР

Заявка № 3267411 Приоритет изобретения 30 марта 1981г.

Зарегистрировано в Государственном реестре изобретений СССР

14 октября 1982г.

Действие авторского свидетельства распространяется на всю территорию Союза ССР.

Председатель Комитета

Начальник отдела

ЖПФ Госпатент, 1979. Зак. 79-3083.

Certificate on innovation

(*Aurthor's certificate № 997281)*

Subject:

Method of differential diagnostics of prostate diseases

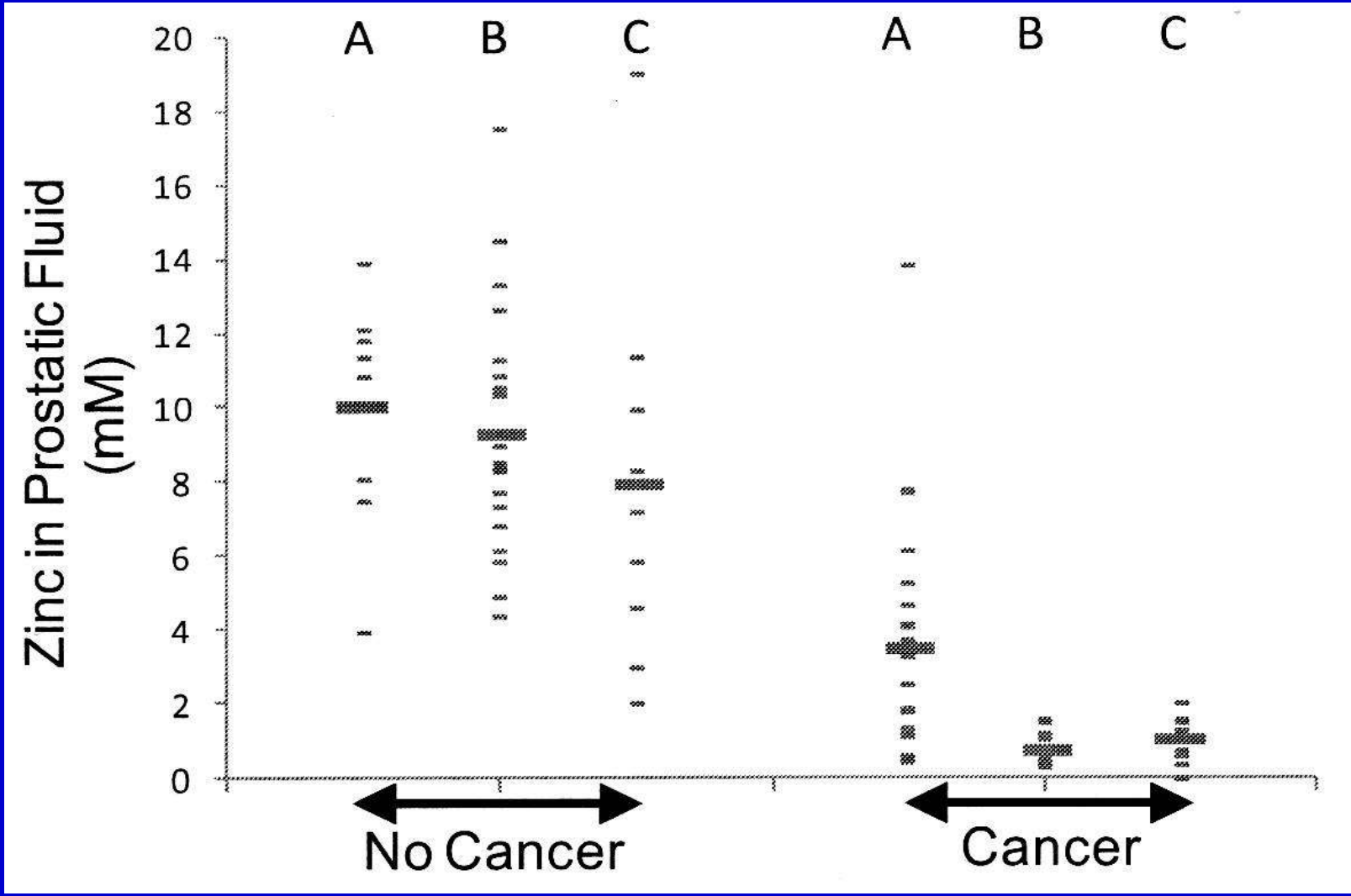
Author:

Zaichick et al.

Date:

30 March 1981

Fig.4.2. Comparison of our results with other data on using Zn content in expressed prostatic fluid for PCa diagnostics



A – NeuroBioTex. USA, 2007, n=87

B – Zaichick et al., Russia, 1997 (end of 70th) , n=91

C – Gomez et al., Venezuela, 2007, n=20

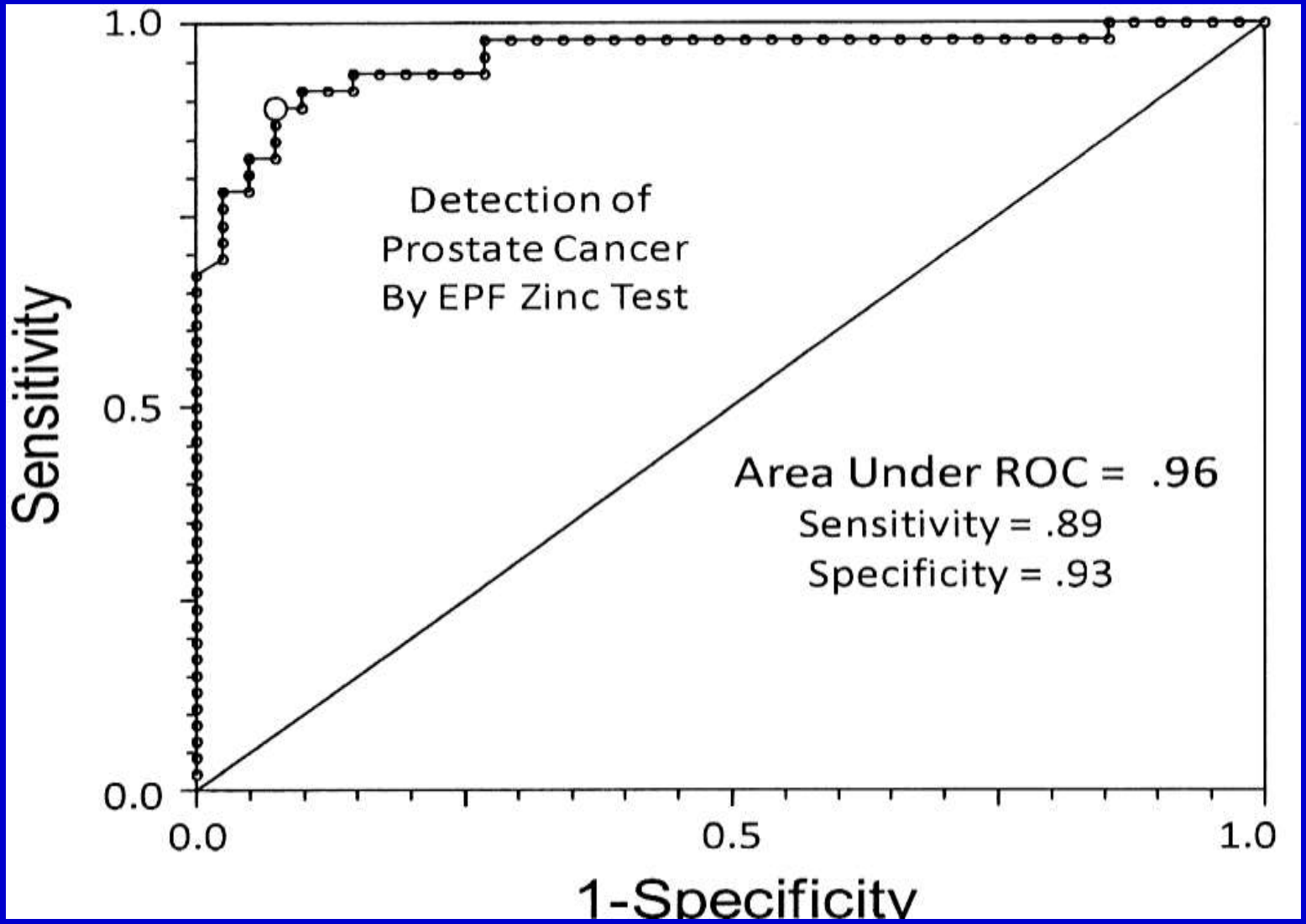


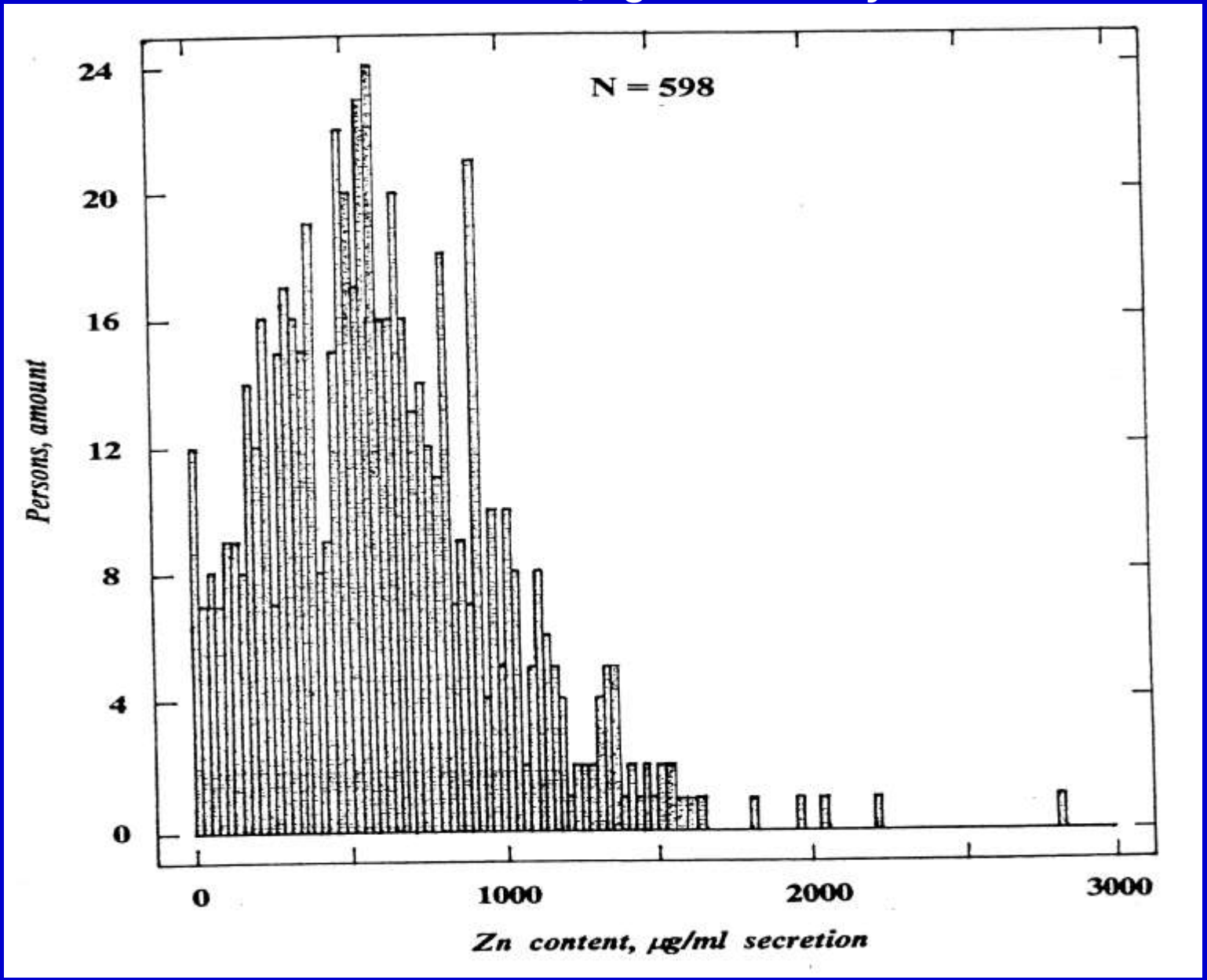
Fig.4.3. The data shown in Fig. 4.2. were combined and analysed by the Receiver Operating Curve (ROC) analysis and the result plotted here. All data points fron three separate studies were included.

EDXRF application in the early prostate cancer diagnostics

In the 1985 year we used only Zn-test for prostate cancer screening of 598 men, Obninsk residents, aged above 60. A transrectal digital massage of the prostate was used to obtain a drop of prostatic fluid. A EDXRF device developed for the analysis of biopsy material was used to determine the content of zinc in prostatic fluid. A group with zinc level lower than 100 μg/ml made up 34 subjects. All of them were invited to the Department of Urology for more detailed examination under hospital conditions. However, only 11 persons accepted invitation to be examined. According to common clinical, X-ray, ultrasonography and biopsy data, the prostate cancer was diagnosed for 4 of them. Thus, the probability of cancer cases in the risk group formed on the basis of zinc secretion data approaches 40%. In the other words, the amount of wrongfully positive conclusions about 60% that were at least not worse than PSA-test (prostate specific antigen test) data. However, the cost of EDXRF of Zn in prostatic fluid is much less.

Sviridova T., Zaichick V. Proceedings of the 5th All-Union meeting on activation analysis and other radioanalytical methods (Tashkent, May 26-28, 1987). Tashkent 1987, part I, p. 352.

Fig. 4.3. Histogram of Zn concentration in the prostatic fluid of men, Obninsk citizens, aged over 60 years

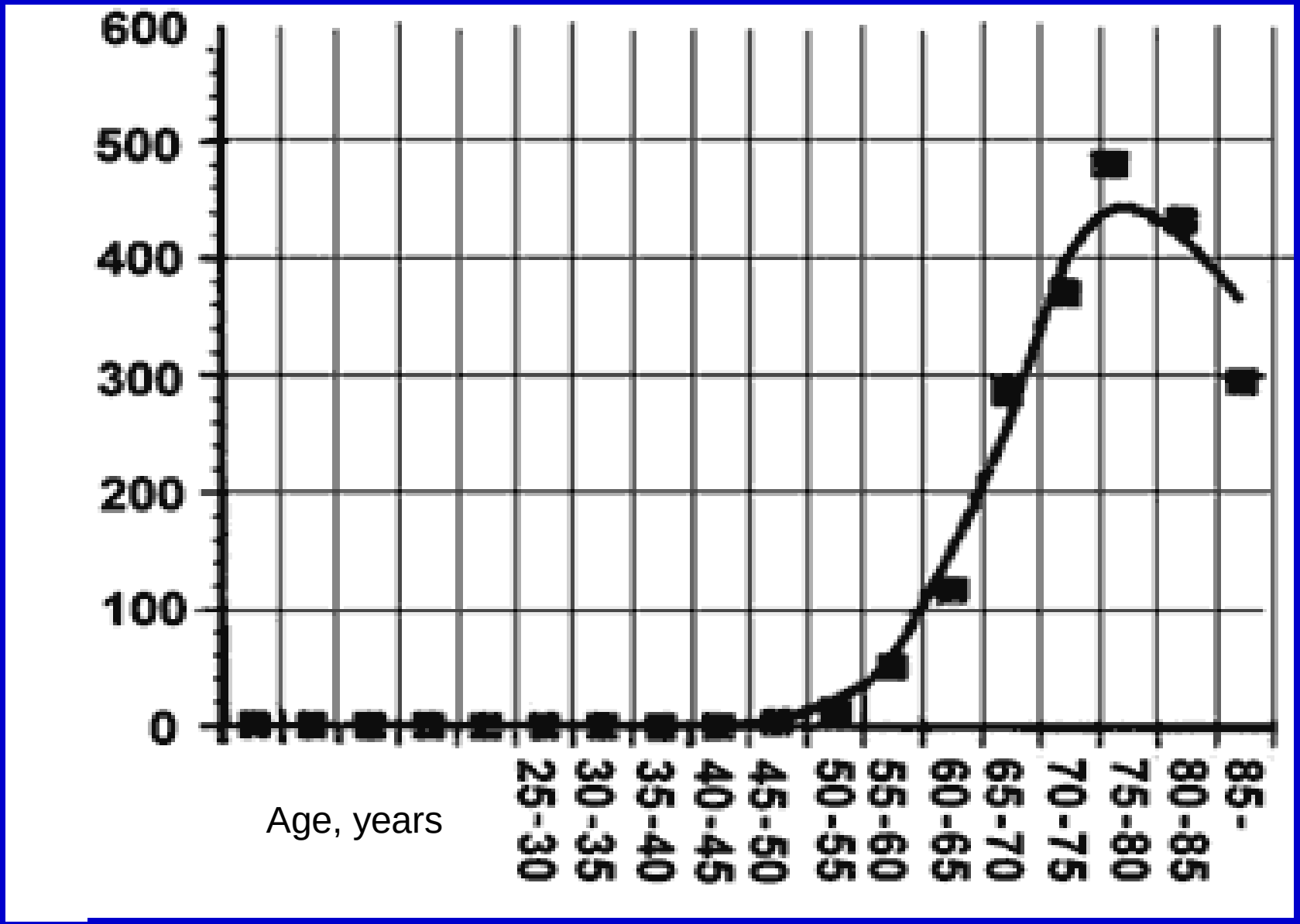


5. Role of Zn in prostate carcinogenesis (the development of cancerous cells from normal ones)

Results of various epidemiological studies make it possible to identify some specific features of prostate cancer:

1. **The possibility of having prostate cancer drastically increase with age, being three orders of magnitude higher for the age group 40–79 years than in those younger than 39 years**.
2. After the age of 40, the incidence of the latent prostate cancer is also rapidly increasing.
3. About 80% of malignant tumours of the prostate are formed within its peripheral zone.
4. The incidence of prostate cancer is greater in developed countries, citizens of which intake a highly caloric protein diet.
5. Occupational contact with zinc as well as its excessive environmental content makes the prostate cancer risk higher.
6. Zn-deficient dairy and vegetable diet was very successful for prostate cancer prevention.
7. A great decrease in mortality from prostate cancer in the course of Se-supplementation was showed.

Incidence rates of prostate cancer per 100,000 population



We studied the effect of age on dynamic changes in content of Zn and some other elements in the prostate fluid of health men resided in the central European part of Russia (n=22, age 18–75 year old). It was shown that Zn concentration in prostatic fluid does not depend on the age of a man, it is 573±177(SD) μg/ml on average (Fig. 5.1). T**his amount is 600 times higher than that in blood serum.**

Our results (mean values, ranges and age-relations) of zinc concentration in prostatic fluid obtained for healthy men correlate well with reported data (Table 5.1).

Table 5.1. Prostatic fluid zinc of healthy men (reference data)

Author	Year	Method	n	Age (Mean, range)	Zinc (μg/ml)
Mackenzie et al.	1962	WDXRF	8	36.6 (25-55)	706±186(SD)*
Anderson et al.	1976	AAS	15	49.5 (30-74)	352±49(SEM)
Fair et al.	1978	AAS	63	52 (24-76)	455±22(SEM)
Homonnai et al.	1978	AAS	12	-	335±13(SEM)
Marmar et al.	1980	AAS	33	-	451±215(SD)
Kavanagh et al.	1985	AAS	152	-	590±220(SD)
Own results	1978	EDXRF	22	48.9 (18-75)	573±177(SD)

*Re-count has made proceeding from the 90.2% water fluid content, AAS - atomic absorption spectrometry, WDXRF – wave dispersive X-ray fluorescent spectrometry, SD - standard deviation, SEM - standard error of the mean

It was shown that Zn concentration in prostatic fluid does not depend on the age of a man

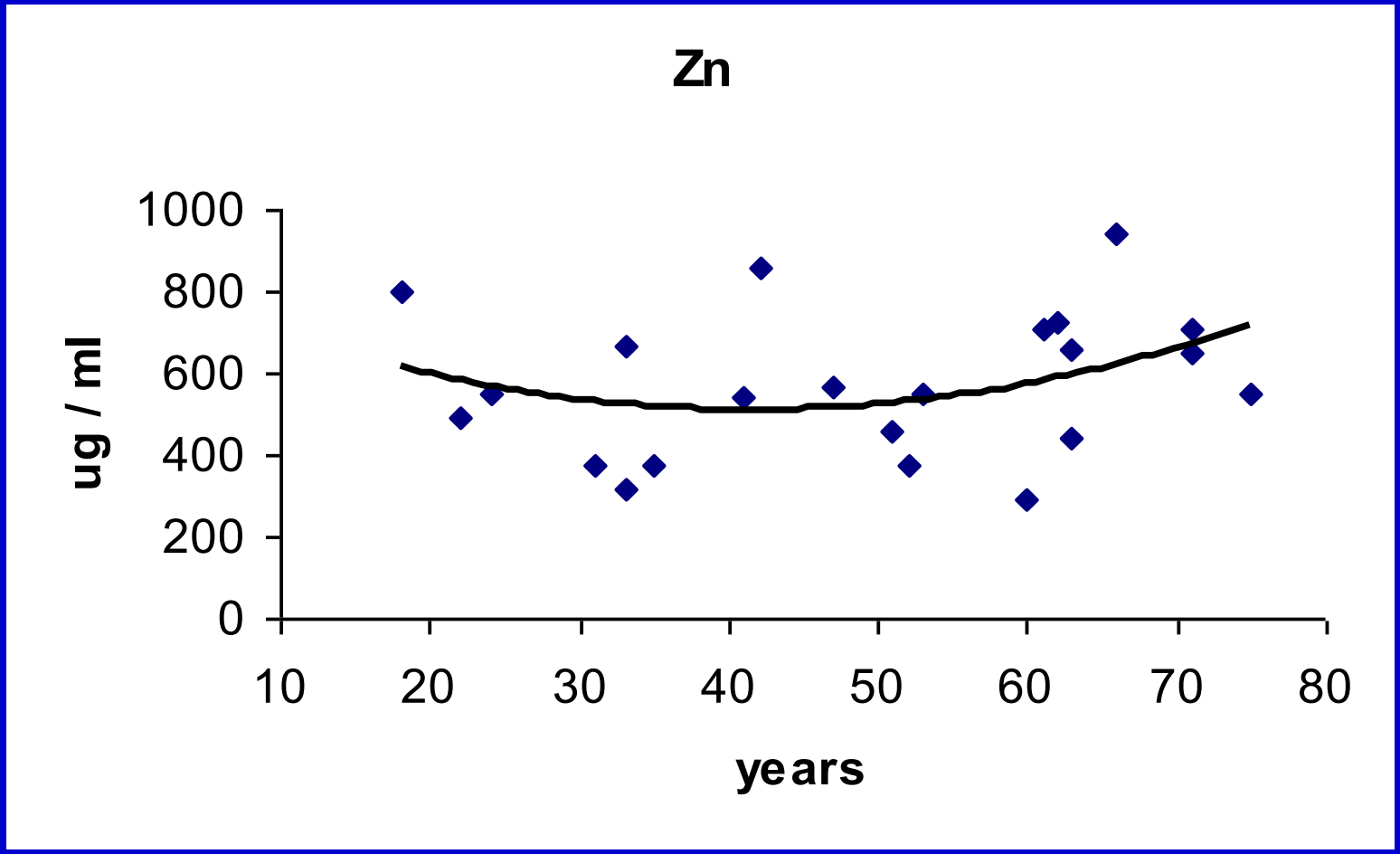
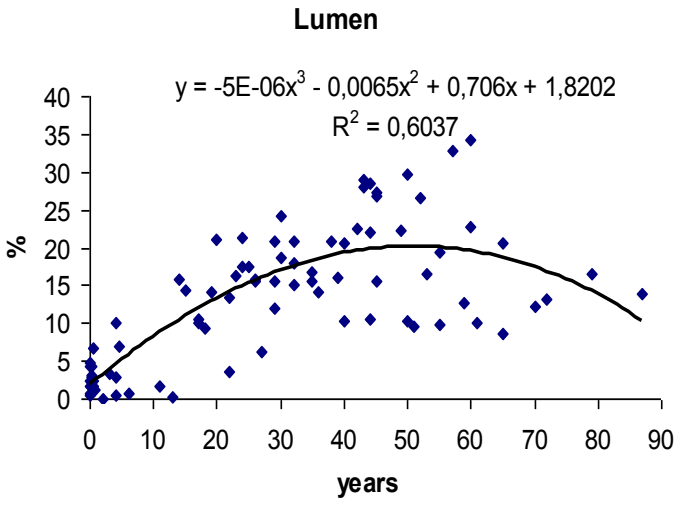
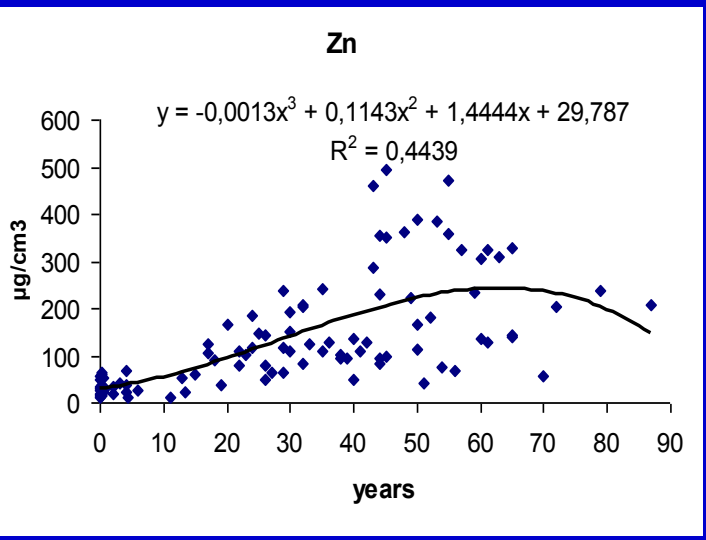
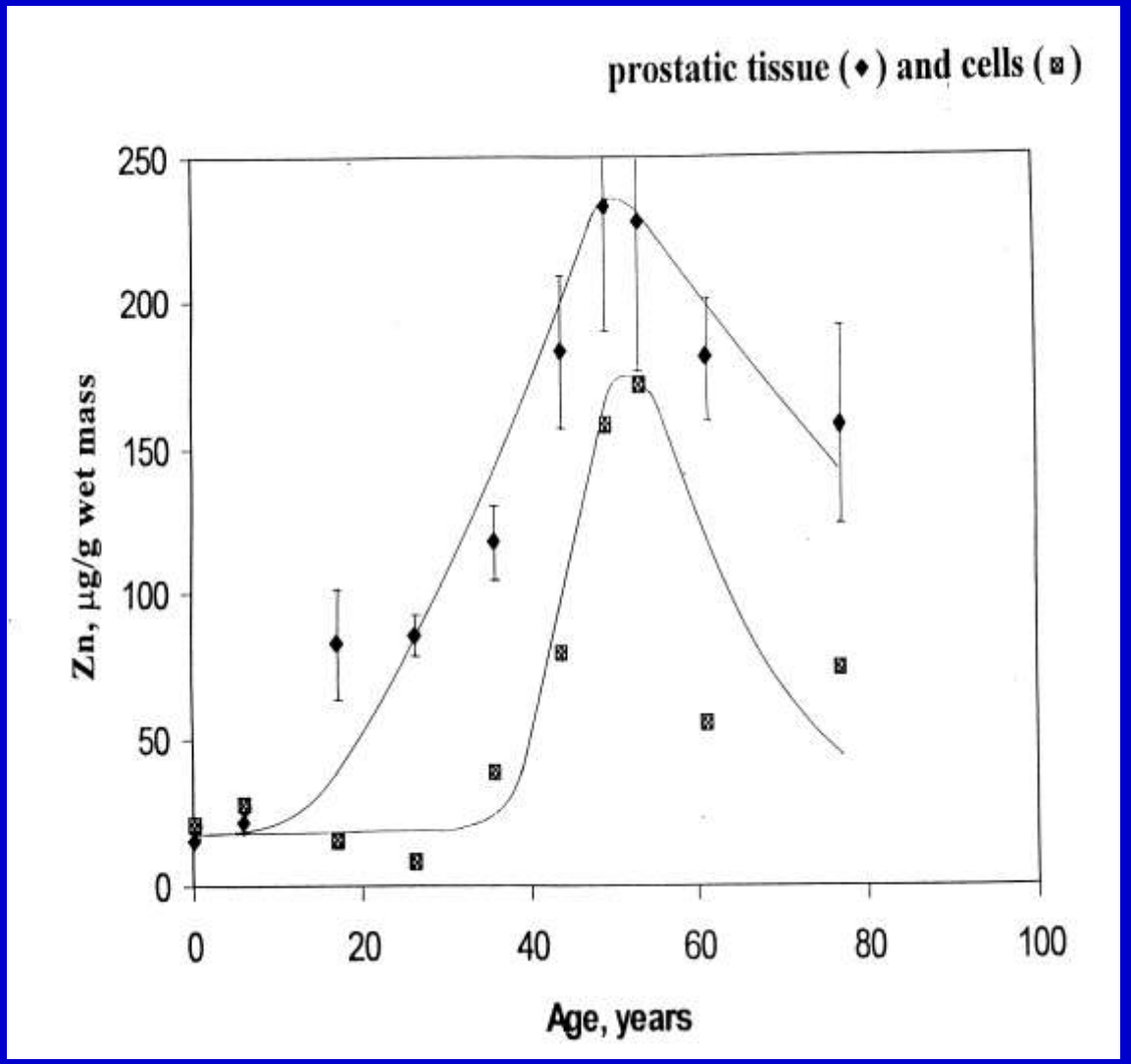


Fig. 5.1. Age-dependence of Zn concentration in the prostate fluid of health men (n=22, age 18–75 year old, μg/ml).

Age-dependence of Zn mass fraction in prostate tissue and prostate cells







A cellular zinc concentration remained at about the same level up to the 40-year age, the value of which did not exceed levels typical of cells of other organs and tissues (Table 1). Intracellular zinc concentration increases drastically after the age of 40, and by 50 to 55 years old it is over 15-fold higher, on the average, than the level typical of men aged 20 to 30.

Table 5.2. The mean and the range of zinc mass fraction in erythrocytes and some soft tissues of health human body (μg/g wet mass)

No	Cells or tissue	Mean	Range
1.	Erythrocytes , μg/ml	14.2	7.6-16.1
2.	Heart	-	17.8-41.5
3.	Kidney	49	25-67
4.	Liver	61	31-78
5.	Lung	15.8	10.0-23.1
6.	Muscle (skeleton)	58.2	38.7-70.0
7.	Pancreas	-	23.4-43.6
8.	Skin	-	6.1-19.5
9.	Spleen	-	14.0-44.4
10.	Stomach	20	11.6-33.1
11	Thyroid	23	24-37

A drastic increase in the incidence of clinical prostate cancer in men aged over 50 can be related to an excessively high intracellular concentration of zinc. It is known that zinc inside epithelial and fibromuscular cells of the prostate is mainly accumulated by the nuclei. By now much data has been stored related to both direct and indirect action of zinc on the DNA polymeric organisation, replication and lesions, and to its vital role for cell division. **These facts allow us to assume that excessive intracellular concentrations of zinc are probably one of the main endogenic factors acting at both initiation and promotion stages of prostate carcinogenesis**.

The assumed hypothesis on the role of excessive intracellular zinc concentration is an explanation to many specific epidemiological features of the prostate cancer. Thus, the age-dependence of incidence of latent and clinical prostate cancer agrees well with age dynamics of intracellular zinc accumulation. Preferential tumour localisation in the peripheral zone of the gland is associated with that that, first of all, an excessive intracellular zinc concentration takes its origin right in that prostate zone. Meat is the main source of zinc in food and this results in a considerably higher incidence of prostate cancer in countries, citizens of which intake a highly caloric protein diet including great amount of meat. Since Se and Zn are antagonists, a successful use of Se-supplementation for the prevention of prostate cancer becomes understandable too. It is also clear that a Zn-deficient diet is efficient for the prevention of prostate cancer because such a diet decreases a possible incidence of excessive zinc concentration in prostatic cells.

Zaichick V. et al. Role of zinc in prostate cancerogenesis. Friedrich-Schiller-Universitat, Jena, 1999, pp.104-115

Zaichick V. J. Radioanal. Nucl. Chem., 2004, **262**, 1, 229-234

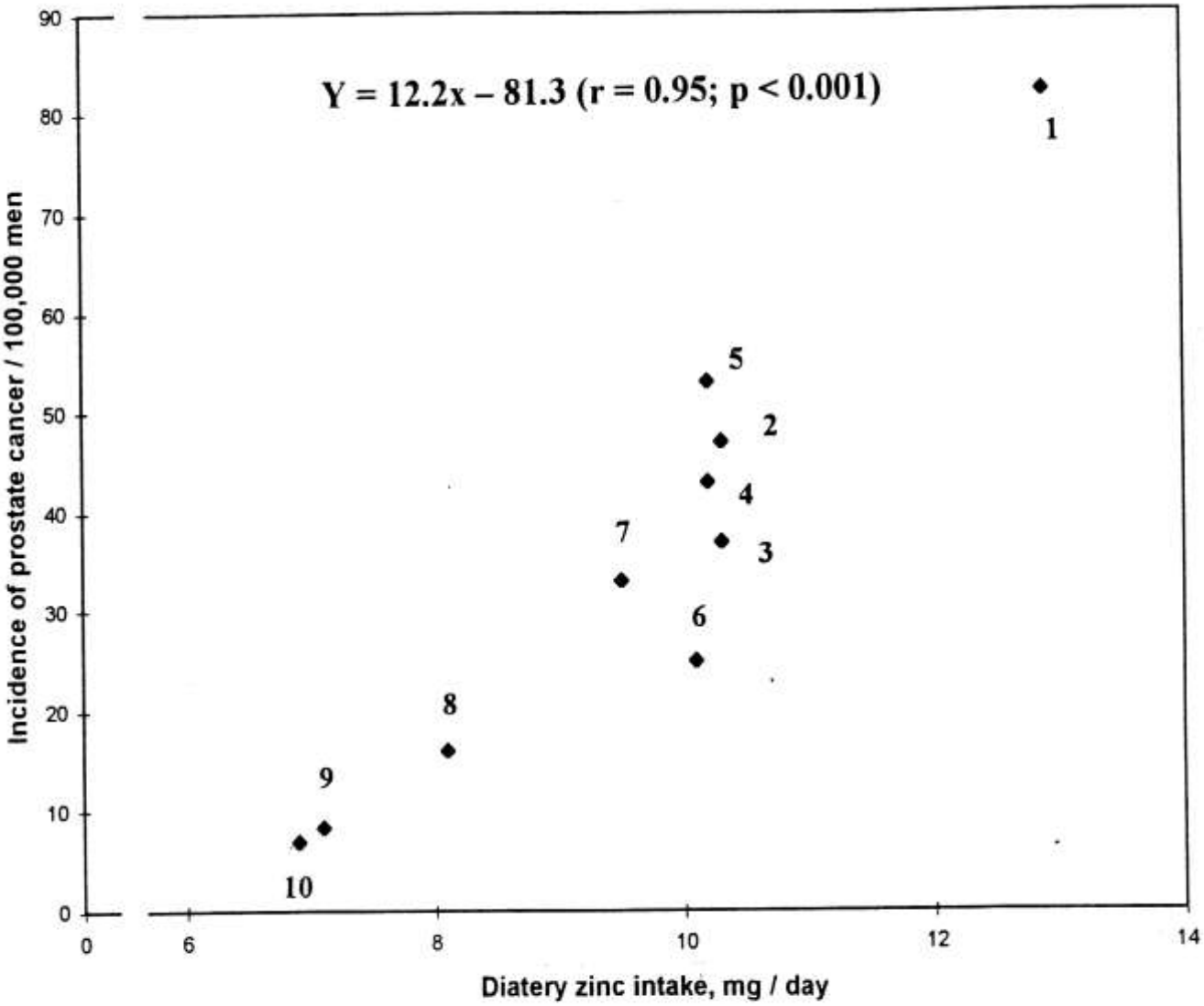


Fig. Correlation between the incidence of prostate cancer and dietary zinc intake in different countries: 1 - USA, 2 - Sweden, 3 - Italy, 4 - Canada, 5 - Switzerland, 6 - England, 7 - Germany, 8 - Yugoslavia, 9 - Japan, 10 - India

Naturally, prostate cancer is a multietiological and multifactorial complex of diseases. The role of excessive intracellular zinc concentration at both initiation and promotion stages of prostate carcinogenesis does not exclude the influence of other factors.

6. Chemical element contents in normal human prostate

The involvement of trace-elements in the etiology of PCa has been debated for almost five decades. It is likely that elevated levels of some metals Ca, Cd, Cr, Cu, Fe, Hg, Mg, Mn, Ni, Pb, V and Zn and a lowered level of Se in prostate tissue possibly initiate and promote PCa. The main hypothesis of the molecular mechanisms involved in prostate tumorigenesis is oxidative DNA damage generated by free radicals of these metals. However, Se compounds have chemopreventive properties for PCa. Metals mentioned above may also be mutagenic through other mechanisms, e.g., by interacting with DNA and they can inhibiting the Zn finger domains featured in most DNA repair proteins.

In the prostate, Zn is accumulated at up to 10-fold higher levels than in other tissues and plays an important role in that organ functions. In our recent study with using EDXRF, INAA-SL, INAA-LL, ICP-AES, and ICP-MS methods it was shown that not only Zn but some other chemical element mass fractions in the human prostate tissue are more than two-three fold higher than in other soft tissues.

Zaichick, S., Zaichick, V. X-Ray Spectrom., 2011,Vol. 40, No 6, pp. 464-469
Zaichick S., Zaichick V. J. Radioanal. Nucl. Chem., 2011, Vol. 288, No 1, pp. 197-202
Zaichick S., Zaichick V. Applied Radiation and Isotopes, 2011, Vol. 69, pp. 827-833
Zaichick V. et al. Biol. Trace Elem. Res., 2012, Vol. 147, No 1, pp. 49–58.
Zaichick V. et al. Biol. Trace Elem. Res., 2012, Vol. 149, No 2, pp. 171-183

Results of EDXRF

Table 6.1. The differences between the mean chemical element contents in the prostate (M±SEM) and in skeletal muscle, liver, and whole blood of Reference Man (mg/kg, on dry weight basis)

Element	This work	Reference Man [Reference]			Ratios, *p* (t-test)		
	Prostate	Muscle [62]	Liver [63]	Whole Blood [63]			
	I	II	III	IV	I / II	I / III	I / IV
Br	35.5±4.0	-	5.2	23.2	-	**6.83**	1.53
Fe	107±5.4	160	720	2300	0.67	0.15	0.047
Rb	17.1±0.8	28.6	17.2	15.5	0.60	0.99	1.10
Sr	1.94±0.32	0.21	0.18	0.28	**9.24**	**10.8**	**6.93**
Zn	850±79	276	172	33.5	**3.08**	**4.94**	**25.4**

*Values in **bold*** have ratio magnitude >2.0

Results of NAA - SL

Table 6.2. The differences between the mean chemical element contents in the prostate (M±SEM) and in skeletal muscle, liver, and whole blood of Reference Man (mg/kg, on dry weight basis)

Element	This work	Reference Man [Reference]			Ratios, *p* (t-test)		
	Prostate	Muscle [62]	Liver [63]	Whole Blood [63]			
	I	II	III	IV	I / II	I / III	I / IV
Br	31.6±3.2	-	5.2	23.2	-	**6.08**	1.36
Ca	2153±166	314	324	314	**6.86**	**6.65**	**6.86**
Cl	12670±675	3430	2890	14880	**3.69**	**4.38**	0.85
K	12014±400	12619	7552	9794	0.95	1.59	1.23
Mg	1150±75	952	586	253	1.21	1.96	**4.55**
Mn	1.56±0.09	0.67	5.17	0.052	**2.33**	0.30	30
Na	10522±343	5952	3448	10825	1.77	**3.05**	0.97

*Values in **bold*** have ratio magnitude >2.0

Results of NAA - LL

Table 6.3. The differences between the mean chemical element contents in the prostate (M±SEM) and in skeletal muscle, liver, and whole blood of Reference Man (mg/kg, on dry weight basis)

Element	This work	Reference Man [Reference]			Ratios, *p* (t-test)		
	Prostate	Muscle [62]	Liver [63]	Whole Blood [63]	I / II	I / III	I / IV
	I	II	III	IV			
Ag	0.0570±0.0067	0.15	0.069	0.036	0.38	0.83	1.58
Co	0.0362±0.0029	0.076	0.31	0.0041	0.47	0.11	**8.8**
Cr	0.483±0.055	0.048	0.097	-	**10.1**	**4.98**	-
Fe	96.9±6.2	160	720	2300	0.61	0.13	0.042
Hg	0.0450±0.0061	0.33	0.31	0.057	0.14	0.15	0.79
Rb	12.5±0.6	28.6	17.2	15.5	0.44	0.73	0.81
Sb	0.0504±0.0048	0.14	0.052	-	0.36	0.96	-
Sc	0.0198±0.0029	-	0.018	0.003	-	1.10	**6.6**
Se	0.633±0.031	0.81	1.12	0.57	0.78	0.57	1.11
Zn	548±55	276	172	33.5	1.99	**3.19**	**16.1**

*Values in **bold*** have ratio magnitude >2.0

Results of ICP-AES

Table 6.4. The differences between the mean chemical element contents in the prostate (M±SEM) and in skeletal muscle, liver, and whole blood of Reference Man (mg/kg, on dry weight basis)

Element	This work	Reference Man [Reference]			Ratios, *p* (t-test)		
	Prostate	Muscle [62]	Liver [63]	Whole Blood [63]			
	I	II	III	IV	I / II	I / III	I / IV
Al	35.8±3.7	1.5	0.0040	0.025	**24**	**9000**	**1440**
B	0.97±0.13	0.33	<0.36	0.175	**2.9**	**>2.85**	**5.54**
Ba	1.18±0.12	0.09	0.14	0.35	**13.1**	**8.43**	**3.37**
Ca	2178±160	314	324	314	**6.94**	**6.72**	**6.94**
Cu	10.7±0.9	10.7	22	4.8	1.0	0.49	**2.23**
Fe	122±5	160	720	2300	0.76	0.17	0.05
K	12530±364	12619	7552	9794	0.99	1.66	1.28
Li	0.040±0.004	0.023	<0.001	0.0007	1.74	**>40**	**57.1**
Mg	1104±70	952	586	253	1.16	1.88	**4.36**
Mn	1.53±0.09	0.67	5.17	0.052	**2.28**	0.30	**29.4**
Na	10470±320	5952	3448	10825	1.76	**3.04**	0.97
P	7580±305	6980	7900	2050	1.09	0.96	**3.70**
S	8717±182	8190	10070	9000	1.06	0.87	0.97
Sr	1.85±0.28	0.21	0.18	0.28	**8.81**	**10.3**	**6.61**
V	≤0.22	0.056	0.05	0.0015	**≤3.9**	**≤4.4**	**≤147**
Zn	782±97	276	172	33.5	**2.83**	**4.55**	**23.3**

Values in ***bold*** have ratio magnitude >2.0

Results of ICP-MS

Table 6.5. Differences between the mean chemical element contents in the prostate (M±SEM) and in skeletal muscle, liver, and whole blood of Reference Man (mg/kg, on dry weight basis)

Element	This work	Median of means for Reference Man [60,61]			Ratios		
	Prostate (I)	Muscle (II)	Liver (III)	Whole Blood (IV)	I / II	I / III	I / IV
Ag	0.0413±0.0047	0.15	0.069	0.036	0.28	0.60	1.15
Al	36±4	1.5	0.0040	0.025	**24**	**9000**	**1440**
As	≤0.018	0.014	0.034	0.057	≤1.3	≤0.53	0.32
Au	0.0039±0.0007	-	0.00018	0.00016	-	**21.7**	**24.4**
B	0.97±0.13	0.33	<0.36	0.175	**2.9**	**>2.85**	**5.54**
Be	0.00099±0.00006	-	-	-	-	-	-
Bi	0.0209±0.0090	0.033	0.014	0.046	0.64	1.49	0.45
Br	28.7±3.1	-	5.2	23.2	-	**5.52**	**4**
Cd	0.781±0.089	0.33	4.3	0.0039	**2.4**	0.18	**200**
Ce	0.0280±0.0038	-	0.21	-	-	0.13	-
Co	0.0347±0.0025	0.076	0.31	0.0041	0.46	0.11	**8.46**
Cr	≤0.64	0.048	0.097	-	**≤13.3**	**≤6.60**	-
Cs	0.0342±0.0023	0.14	0.045	0.014	0.24	0.76	**2.44**
Dy	0.00312±0.00052	-	-	-	-	-	-
Er	0.00181±0.00036	-	-	-	-	-	-
Eu	≤0.0006	-	-	-	-	-	-
Ga	≤0.08	0.0014	0.0024	-	**≤57**	**≤33.3**	-
Gd	0.00304±0.00050	-	-	-	-	-	-
Hf	≤0.02	-	-	-	-	-	-
Hg	0.0463±0.0059	0.33	0.31	0.057	0.14	0.15	0.81
Ho	0.00056±0.00008	-	-	-	-	-	-
Ir	≤0.0004	-	-	-	-	-	-
La	0.074±0.015	-	0.28	-	-	0.26	-
Li	0.040±0.004	0.023	<0.0036	0.0035	1.74	**>11.1**	**11.4**
Lu	≤0.00028	-	-	-	-	-	-
Mn	1.53±0.086	0.47	5.4	0.05	**3.26**	0.28	**30.6**
Mo	0.303±0.030	-	2.1	0.010	-	0.14	**30.3**
Nb	0.00511±0.00086	0.14	0.14	-	0.037	0.037	-
Nd	0.0132±0.0018	-	-	-	-	-	-
Ni	4.31±0.68	0.95	0.10	0.015	**4.54**	**43.1**	**287**
Pb	1.76±0.38	0.48	1.6	0.52	**3.67**	1.1	**3.38**
Pd	≤0.007	-	-	-	-	-	-
Pr	0.00334±0.00044	-	-	-	-	-	-
Pt	≤0.0009	-	0.11	-	-	-	-
Rb	15.9±0.6	28.6	17.2	15.5	0.56	0.92	1.03
Re	≤0.0015	-	-	-	-	-	-
Sb	0.0402±0.0047	0.14	0.052	-	0.29	0.77	-
Se	0.730±0.032	0.81	1.12	0.57	0.90	0.65	1.28
Sm	0.00268±0.00038	-	-	0.041	-	-	0.065
Sn	0.246±0.045	0.52	1.90	-	0.47	0.13	-
Ta	≤0.005	-	-	-	-	-	-
Tb	0.00043±0.00009	-	-	-	-	-	-
Te	<0.0025(DL)	3.00	-	0.028	≤0.001	-	0.089
Th	0.00243±0.00048	-	-	0.0026	-	-	0.93
Tl	0.00141±0.00011	0.24	0.19	0.0020	0.0059	0.0074	0.705
Tm	0.00030±0.00006	-	-	-	-	-	-
U	0.0049±0.0014	0.00095	0.0010	0.000016	**5.12**	**4.9**	**306**
Y	0.0192±0.0033	0.019	-	0.024	1.01	-	0.80
Yb	0.00146±0.00024	-	-	-	-	-	-
Zn	782±97	276	172	33.5	**2.83**	**4.55**	**23.3**
Zr	0.0444±0.0085	0.095	0.103	0.049	0.47	0.43	0.91

Values in ***bold*** have ratio magnitude >2.0

Our data reveal that the human prostate accumulates not only Zn but also such trace-elements as Al, Au, B, Ba, Br, Ca, Cd, Co, Cr, Cs, Cu, Li, Mg, Mn, Mo, Ni, P, Pb, Sc , Sr, U и V.

The results given here, for the first time of mass fraction contents of about 70 chemical elements in the normal prostate, are believed to provide an essential basis for future studies of their involvement in prostatic metabolism and pathophysiology.

Conclusion

Nuclear analytical methods are the powerful analytical tools for the determination of chemical element content in prostate tissue. The methods can be successfully used both in experimental and clinical studies of benign prostatic hyperplasia and prostate cancer.

Thank you very much, indeed, for your attention !