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Review

A Systematic Review of the Calcium Content of the Normal Human Prostate Gland

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ABSTRACT

Introduction: There is much lack of knowledge concerning most prostatic malfunction, especially the reasons and detailed nature of its pathologies. In spite of advances in medical science, the differential diagnosis of prostatic pathologies has steadily increased in complexity and controversy. A proposal has been made that prostatic calcium (Ca) content determinations may aid in resolving these issues for prostate disorders and especially as an indicator of its carcinoma risk. As a result many measurements of normal prostatic Ca have been made.

Materials and methods: Here we analyze data published concerning Ca prostatic levels in healthy subjects. In all 1911 items in the literature of the years dating back to 1921 were identified in the following databases: PubMed, the Cochrane Library, Scopus, Web of Science and ELSEVIER-EMBASE. This data was subject to an analysis employing both the "range" and "median" of means. In this way the disparate nature of published Ca content of normal prostates was evaluated. From the papers examined, 36 were selected for the objective analysis of data from their 1357 healthy patients..

Results: On a wet mass basis prostatic Ca levels spanned the interval from 73 mg/kg to 1280 mg/kg with 360 mg/kg as the median of their means. It is accepted that the prostatic Ca content is contingent on a wide variety of aspects of the host's milieu, including androgen levels, zone of human prostate sampled, relative amounts of different types of prostatic tissue studied, Ca content of food and drink, Ca supplement intake, age, and the method of analysis.

Conclusions: The data encompassed a wide range of values and the sample was small, hence it is advisable that further studies be performed.

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1. INTRODUCTION

Amongst the many pathological prostatic conditions, prostatic carcinoma (PCa), chronic prostatitis and benign prostatic hyperplasia (BPH) are very frequently encountered, especially in the elderly [1-3]. Their causes and pathogenesis are poorly understood. Moreover, despite technological advances, the differential diagnosis of

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prostate disorders has become progressively more complex and controversial. An improvement of this situation, especially recognition of relevant risk factors and the disorders' etiologies can allow great reduction in the incidence of these prostatic disorders [4].

We have previously shown that calcium (Ca) and some trace elements (TEs), including Zn, can significantly affect prostatic function [5-16]. Also published results indicate that prostatic Ca can play a significant role in etiology of PCa [17]. Further, the value of Ca level and the level ratio Zn/Ca and Ca/TEs as biomarkers of prostate pathology has been established [18-28].

The effects of Ca and all TEs are related to their concentration. Recorded observations range from a deficiency state, through normal function as biologically essential components, to an imbalance, when excess of one element interferes with the function of another, to pharmacologically active concentrations, and finally to toxic and even life-threatening concentrations [29]. In this context, significant correlations between high Ca intake and the risk of prostate cancer have been reported [30-33]. Investigation of the role of Ca in carcinogenesis is a long story [34]. Recently, there have been a number of developments in the fields of Ca and nuclear signaling in PCa, however, precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states have yet to be fully defined. Ca homeostasis mechanisms are critically involved in both normal function and cancerous transformation of prostate epithelial cells. Therefore, current models propose that dysregulated Ca homeostasis in tumoral cells depends on changes in the ratio of influx/efflux and storage of Ca, compared with normal cells, may contribute to Ca-induced prostate carcinogenesis [35-37]. Homeostasis mechanisms of intra-prostatic Ca metabolism cause stable level of this element in normal functional conditions of the prostate. Thus, the Ca content in prostate tissue is an important parameter of the gland function.

Table 1. Reference data of Ca mass fractions (mg/kg wet tissue) in "normal" human prostatic tissue

Reference	Method	n	Age M(Range)	Sample preparation	Ca	
					Mean±SD	Range
ICRP 1960 [38]	=	=	=	=	320	-
Zakutinsky et al. [39]	-	-	-	-	320	-
Tipton et al. 40]	AES	40	Adult	D, A	240±130	-
Schroeder et al. [41]	AAS	1	Adult	A, AD	320	-
Hienzsch et al. [42]	AAS	110	<1-90	A, AD	140-260	-
Schneider et al. [43]	AAS	21	16-37	A, AD	73±20	-
Soman et al. [44]	AAS	3	Adult	A, AD	290±180	-
Holm et al. [45]	AAS	21	16-37	A, AD	73±20	-
Forssen [46]	XRF	12	Adult	A, AD	240	140-330
Schroeder et al. [47]	AES	198	Adult	D, A	Med. 210	-
Kwiatek et al. [48]	SRIXE	3	61	CS (NB)	320±40	-
Kwiatek et al. [49]	SRIXE	1	-	CS (NB)	120	-
Guntupalli et al. [50]	PIXE	27	53(38-68)	Pressing	766±12	-
Sapota et al. [51]	AAS	11	49-67	AD	305±66	-
Tohno et al. [52]	ICPAES	57(J)	65-101	F,FF,W,AD	1280±2090	-
Zaichick et al. [53]	NAA	9	13-20	Intact	190±140	68-1170
		28	21-40	Intact	360±150	-
		27	41-60	Intact	440±270	-
Zaichick et al. [54]	ICPAES	9	13-20	AD	220±130	68-1170
		AD	360±140	-	28	21-40
		27	41-60	AD	440±260	-
Zaichick et al. [7]	NAA	16	20-30	Intact	370±80	-
Zaichick et al. [9]	NAA+ICPAES	16	20-30	Intact, AD	400±290	-
Leitao et al. [55]	SR-TXRF	8	18-30	AD	460±210	-
Zaichick et al. [56]	NAA	28	21-40	Intact	340±120	160-530
		27	41-60	Intact	410±160	210-830
		10	61-87	Intact	320±60	240-400
Zaichick et al. [57]	NAA+ICPAES	28	21-40	Intact, AD	360±140	160-700
		27	41-60	Intact, AD	440±230	200-1170
		10	61-87	Intact, AD	330±100	220-530
Zaichick et al. [12]	NAA	29	0-13	Intact	260±150	-
		21	14-30	Intact	410±350	-
Zaichick et al. [13]	NAA+ICPAES	29	0-13	Intact, AD	240±150	-
		21	14-30	Intact, AD	430±340	-
Zaichick et al. [14]	NAA+ICPAES	16	20-30	Intact, AD	400±290	-
Zaichick et al. [58]	NAA	32	44-87	Intact	390±150	210-830
Zaichick [59]	NAA+ICPAES	65	21-87	Intact, AD	390±180	-
Zaichick et al. [60]	NAA	37	41-87	Intact	390±150	210-830
Zaichick et al. [61]	NAA	37	56±11	Intact	410±210	200-1170
Zaichick et al. [62]	NAA	37	41-87	Intact	390±150	210-830
Zaichick et al. [63]	NAA+ICPAES	37	41-87	Intact, AD	410±210	200-1170
Zaichick et al. [64]	NAA+ICPAES	32	44-87	Intact, AD	410±210	200-1170
Zaichick et al. [65]	NAA+ICPAES	37	41-87	Intact, AD	410±210	200-1170
Zaichick et al. [66]	NAA+ICPAES	37	41-87	Intact, AD	502±337	234-1980
Zaichick [67]	NAA+ICPAES	37	41-87	Intact, AD	410±210	200-1170
Zaichick et al. [68]	NAA+ICPAES	37	41-87	Intact, AD	410±210	200-1170
Median of means: 365. Range of means (M_{min} - M_{max}): 73-1280. Ratio M_{max}/M_{min}: 17.5.						

M: Arithmetic mean; SD: Standard deviation of mean; AES: Atomic emission spectrometry; AAS: Atomic absorption spectrophotometry; XRF: X-ray fluorescence; SRIXE: Synchrotron radiation-induced X-ray emission; PIXE: Proton induced X-ray fluorescence; ICPAES: Inductively coupled plasma atomic emission spectrometry; SR-TXRF: Total reflection X-ray fluorescence spectroscopy using synchrotron radiation technique; NAA: Neutron activation analysis; D: Drying at high temperature; A: Ashing; AD: Acid digestion; CS: Cut section on a cryomicrotome; F: Fixed in ethanol, chloroform, formaldehyde; FF: Defatted (fat free); W: Washing; NB: Needle biopsy; J: Japanese; T: Thai.

To date, the Ca content of both abnormal and normal prostates has been listed in many publications. But for

generally accepted Ca levels to be established in a variety of prostatic conditions, more studies are required to resolve existing discrepant reported levels. This work, a systematic review of pertinent literature, may also offer further understanding into the means of diagnosis and etiology of some prostatic conditions, because of the present statistical study of normal prostates in terms of their Ca content.

2. MATERIALS AND METHODS

2.1. DATA SOURCES AND SEARCH STRATEGY

To identify the most pertinent articles on which this review is based, a detailed and methodical search of the web's PubMed, the Cochrane Library, Scopus, Web of Science and ELSEVIER-EMBASE databases was undertaken. The author's personal archive, amassed (using combinations of the keywords: prostatic trace elements, prostatic Ca content, prostatic tissue) in the years from 1966 to the present, was also used. As an example of the method employed, the search terms: "Ca content", "Ca level", "prostatic tissue Ca", "Ca mass fraction" and "Ca of prostatic tissue" were used to determine data to provide Ca prostatic content. There were no restrictions on the language of articles sought. Close evaluation of the article's title, determined its potential for acceptability. In addition references quoted in the article proved a further valuable source of relevant data.

2.2. ELIGIBILITY CRITERIA

For evaluation of a paper, a necessary condition for acceptance was presentation of quantitative Ca prostatic content. A further necessary condition for inclusion was that all subjects in a normal or control group were males in good health without any history or indications of urological or andrological dysfunction and that they provided samples of prostate tissue from which Ca levels were determined.

2.3. EXCLUSION CRITERIA

All case reports were excluded, as were studies of subjects who were using Ca supplementation.

2.4. DATA EXTRACTION

From each paper evaluated relevant data was extracted using a standardized protocol. The information so removed for further study comprised the following; the ages and numbers of the healthy persons studied, methods of sample preparation and Ca content measurement, the ranges of Ca levels and their means, medians and standard deviations of the mean. Entire articles and their abstracts were evaluated separately. Any apparent difference between them resulted in revaluations of the complete text until there was resolution of any discrepancies.

2.5. STATISTICAL ANALYSIS

Studies were combined based on means of Ca levels in prostatic tissue. This analysis was done on data mined from 36 studies, including 1357 persons. The data divergence

Table 2. Reference data of Ca mass fractions (mg/kg wet tissue) in "normal" whole prostate

Reference	Method	n	Age M(Range)	Sample preparation	Ca	
					Mean±SD	Range
ICRP [38]	=	=	=	=	320	-
Zakutinsky et al. [39]	-	-	-	-	320	-
Tipton et al. [40]	AES	40	Adult	D, A	240±130	-
Schroeder et al. [41]	AAS	1	Adult	A, AD	320	-
Hienzsch et al. [42]	AAS	110	<1-90	A, AD	140-260	-
Schneider et al. [43]	AAS	21	16-37	A, AD	73±20	-
Soman et al. [44]	AAS	3	Adult	A, AD	290±180	-
Holm et al. [45]	AAS	21	16-37	A, AD	73±20	-
Forssen [46]	XRF	12	Adult	A, AD	240	140-330
Schroeder et al. [47]	AES	198	Adult	D, A	Med. 210	-
Sapota et al. [51]	AAS	11	49-67	AD	305±66	-
Tohno et al. [52]	ICPAES	57(J)	65-101	F,FF,W,AD	1280±2090	-
		13(T)	43-86	F,FF,W,AD	750±150	-
Median of means: 290. Range of means (M_{min} - M_{max}): 73-1280. Ratio M_{max}/M_{min}: 17.5.						

M: Arithmetic mean; SD: Standard deviation of mean; AES: Atomic emission spectrometry; AAS: Atomic absorption spectrophotometry; XRF: X-ray fluorescence; ICPAES: Inductively coupled plasma atomic emission spectrometry; D: Drying at high temperature; A: Ashing; AD: Acid digestion; F: Fixed in ethanol, chloroform, formaldehyde; FF: Defatted (fat free); W: Washing; J: Japanese; T: Thai.

was analyzed using both their "range of means" and "median of means". In addition, two subgroups of data were used to evaluate the difference between results obtained for tissue Ca levels in whole gland and in peripheral zone of prostate.

3. RESULTS

Information about Ca levels in prostatic tissue in different prostatic diseases is of obvious interest, not only to understand the etiology and pathogenesis of prostatic diseases more profoundly, but also for their diagnosis, particularly for PCa diagnosis [20, 21, 27]. Thus, it dictates a need for reliable values of the Ca levels in the prostatic tissue of apparently healthy subjects, ranging from young adult males to elderly persons.

A total of 1911 individual studies were identified. Among them 36 studies were ultimately selected according to eligibility criteria that investigated Ca levels in tissue of normal prostates (Table 1) and these 36 papers [7, 9, 12-14, 38-68] comprised the material on which the review was based. A number of values for Ca mass fractions were not expressed on a wet mass basis by the authors of the cited references. However, we calculated these values using the medians of published data for water - 83% [69-72] and ash - 1% (on a wet mass basis) contents in normal prostates of adult men [40, 41, 71, 73].

Table 3. Reference data of Ca mass fractions (mg/kg wet tissue) in peripheral zone of "normal" human prostate

Reference	Method	n	Age M(Range)	Sample preparation	Ca	
					Mean±SD	Range
Kwiatek et al. [48]	SRIXE	3	61	CS (NB)	320±40	-
Kwiatek et al. [49]	SRIXE	1	-	CS (NB)	120	-
Guntupalli et al. 50]	PIXE	27	53(38-68)	Pressing	766±12	-
Zaichick et al. [53]	NAA	9	13-20	Intact	190±140	68-1170
		28	21-40	Intact	360±150	-
		27	41-60	Intact	440±270	-
Zaichick et al. [54]	ICPAES	9	13-20	AD	220±130	68-1170
		28	21-40	AD	360±140	-
		27	41-60	AD	440±260	-
Zaichick et al. [7]	NAA	16	20-30	Intact	370±80	-
Zaichick et al. [9]	NAA+ICPAES	16	20-30	Intact, AD	400±290	-
Leitao et al. [55]	SR-TXRF	8	18-30	AD	460±210	-
Zaichick et al. [56]	NAA	28	21-40	Intact	340±120	160-530
		27	41-60	Intact	410±160	210-830
		10	61-87	Intact	320±60	240-400
Zaichick et al. 2014 [57]	NAA+ICPAES	28	21-40	Intact, AD	360±140	160-700
		27	41-60	Intact, AD	440±230	200-1170
		10	61-87	Intact, AD	330±100	220-530
Zaichick et al. [12]	NAA	29	0-13	Intact	260±150	-
		21	14-30	Intact	410±350	-
Zaichick et al. [13]	NAA+ICPAES	29	0-13	Intact, AD	240±150	-
		21	14-30	Intact, AD	430±340	-
Zaichick et al. [14]	NAA+ICPAES	16	20-30	Intact, AD	400±290	-
Zaichick et al. [58]	NAA	32	44-87	Intact	390±150	210-830
Zaichick [59]	NAA+ICPAES	65	21-87	Intact, AD	390±180	-
Zaichick et al. [60]	NAA	37	41-87	Intact	390±150	210-830
Zaichick et al. [61]	NAA	37	56±11	Intact	410±210	200-1170
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Zaichick et al. [65]	NAA+ICPAES	37	41-87	Intact, AD	410±210	200-1170
Zaichick et al. [66]	NAA+ICPAES	37	41-87	Intact, AD	502±337	234-1980
Zaichick [67]	NAA+ICPAES	37	41-87	Intact, AD	410±210	200-1170
Zaichick et al. [68]	NAA+ICPAES	37	41-87	Intact, AD	410±210	200-1170
Median of means: 390. Range of means (M_{min} - M_{max}): 120-766. Ratio M_{max}/M_{min}: 6.4.						

M: Arithmetic mean; SD: Standard deviation of mean; SRIXE: Synchrotron radiation-induced X-ray emission; PIXE: Proton induced X-ray fluorescence; ICPAES: Inductively coupled plasma atomic emission spectrometry; SR-TXRF: Total reflection X-ray fluorescence spectroscopy using synchrotron radiation technique; NAA: Neutron activation analysis; AD: Acid digestion; CS: Cut section on a cryomicrotome; NB: Needle biopsy.

Table 1 summarizes general data from the 36 studies. The retrieved studies involved 1357 subjects. The ages of subjects were available for 28 studies and ranged from 0-101 years. Information about the analytical method and sample preparation used was available for 34 studies. Fifteen studies determined Ca levels by destructive (require washing, pressing, cutting section on a cryomicrotome, high temperature drying, ashing, acid digestion, fixation in ethanol/chloroform/formaldehyde, and defatting of tissue samples) analytical methods (Table 1): one using X-ray fluorescence (XRF), one - proton induced X-ray fluorescence (PIXE), one - total reflection X-ray fluorescence spectroscopy using synchrotron radiation technique (SR-TXRF), two - atomic emission spectrometry (AES), two - synchrotron radiation-induced X-ray emission (SRIXE), two - inductively coupled plasma atomic emission spectrometry (ICPAES), and six - atomic absorption spectrophotometry (AAS). Eight studies detected Ca level in intact prostatic tissue samples by nondestructive analytical method, such as neutron activation analysis (NAA). In eleven studies a combination of destructive and nondestructive methods (ICPAES and NAA) was used and results were summarized.

Figure 1 illustrates the data set of Ca measurements in 36 studies during the period from 1960 to 2019.

Table 2 presents data from the 12 studies of Ca mass fraction in the whole prostate gland, while Table 3 summarizes results of Ca mass fraction investigations in peripheral zones of prostates from the 24 publications.

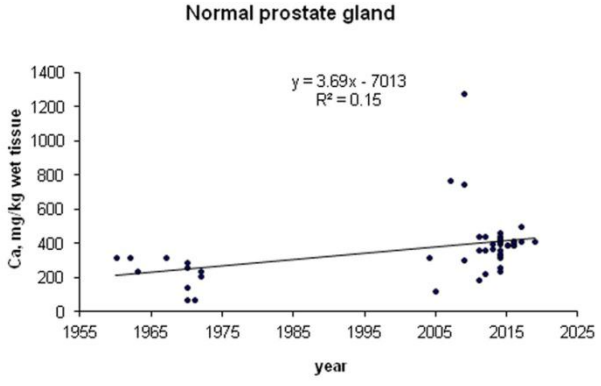

***Figure 1**: Data on Ca content in "normal" prostate tissue reported from 1960 to 2020.*

4. DISCUSSION

The range of means of Ca mass fractions reported in the literature for "normal" prostatic tissue varies widely from 73 mg/kg [45] to 1280 mg/kg [52] with median of means 360 mg/kg wet tissue (Table 1). Thus, the maximal value of mean Ca mass fraction reported in the literature was 17.5 times higher the minimal value of mean Ca mass fraction. This variability of reported mean values can be explained by a dependence of Ca content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, non-homogeneous distribution of Ca levels throughout the prostate gland volume, age, ethnicity, diet, and others. Not all these factors were strictly controlled in the cited studies. For example, in some studies the "normal" prostate means a gland of an apparently healthy man who had died suddenly, but without any morphological confirmation of "normality" of his prostatic tissue. In other studies the "normal" prostate means a non-cancerous prostate (but hyperplastic and inflamed glands were included) and even a visually normal prostatic tissue adjacent to a prostatic malignant tumor. Some researchers used as the "normal" prostate the glands of patients who died from acute and chronic non-prostatic diseases including subjects who had suffered from prolonged wasting illnesses. In some studies whole glands were used for the investigation while in others the Ca content was measured in pieces of the prostate. Therefore published data allowed us to estimate the effect of only some different factors on Ca content in "normal" prostate tissue.

4.1. ANALYTICAL METHOD

Prostate tissue Ca contents showed large variations among published data. In our opinion, the leading cause of inter-observer variability was insufficient quality control of results in published studies. In many reported papers such destructive analytical methods as AES, AAS and ICP-AES were used. These methods require ashing or acid digestion of the samples at a high temperature. There is evidence that use of this treatment causes some quantities of Ca to be lost [29, 74, 75]. On the other hand, the Ca content of chemicals used for acid digestion can contaminate the prostate samples. Thus, when using destructive analytical methods it is necessary to allow for the losses of TEs, for example when there is complete acid digestion of the sample. Then there are contaminations by TEs during sample decomposition, which require addition of some chemicals.

Such analytical methods as SRIXE, PIXE, and SR-TXRF need to use thin sections of prostatic tissue. In the case of a frozen tissue samples, prostatic fluid (a significant pool of Ca content in prostate [17,76-81] may be lost as a result of cutting microscopic sections. And, besides, Ca, particularly from prostatic fluid, may be lost during sample fixation in ethanol/chloroform/formaldehyde.

It is possible to avoid these problems by using non-destructive methods. Such method NAA can be fully instrumental and nondestructive analytical tool because a tissue sample is investigated without requiring any sample pretreatment or its destruction.

It is, therefore, reasonable to conclude that the choice of analytical method and quality control of results are very important factors for using the Ca content in prostatic tissue as biomarkers.

4.2. AGE

In many studies a significant increase in Ca content with increasing of age was shown by the comparison of different age groups or the Pearson's coefficient of correlation between age and Ca content in prostate tissue [7, 9. 10. 12-15, 17, 52-54, 56, 57]. The most detailed investigations of age-dependence of prostatic Zn were done by Zaichick and Zaichick [7, 9, 10, 12-15, 17, 53, 54, 56, 57]. For example, a strongly pronounced tendency for an age-related increase of Ca mass fraction was observed in the prostate for the third to six decades [56, 57]. In prostates of 41-60 year old men, the mean Ca mass fraction was 2 times greater than that in the prostates of young adult males. According to Tohno et al. 2008 [52] in the prostates of Thai subjects ranged in age from 43 to 86 years a significant direct correlation was found between age and Ca content, but it was not found in the prostates of Japanese subjects ranged in age from 65 to 101 years. In the study of Heinzsch et al. 1970 [42] correlations between age and Ca content in prostate of males aged 11-90 years was not found.

4.3. ANDROGEN-DEPENDENCE OF PROSTATIC CA LEVELS

The significant difference between prostatic Ca levels before and after puberty allowed us to conclude that in man androgens govern this metal's content of the prostate [12, 13]. The relationship between prostatic Ca and androgens was indirectly confirmed in Hemelrijck et al. 2013 study serum Ca and sex steroid hormones in the Third National Health and Nutrition Examination Survey (NHANES III) [82]. Thus, the Ca content in normal prostates can possibly depend on the level of androgens. However, studies on direct correlations between the Ca content in normal prostates and the level of androgens were not found.

4.4. NON-UNIFORM DISTRIBUTION OF CA WITHIN THE GLANDULAR VOLUME

The publications on distribution of Ca within the glandular volume were not found. However, data presented in Figure 1 indicated a visible difference between results obtained during periods 1960-1972 and 2004-2019 years. In all studies published in 1960-1972 years the whole glands were used for the prostatic Ca content investigations, while peripheral zones of prostates were mainly involved for this purpose in the recent investigations. Therefore, studies performed on whole prostates and on peripheral zones of prostates were summarized separately in Tables 2 and 3, respectively. A comparison of medians of Ca content means presented in Tables 2 and 3 demonstrated a difference in the distribution of this metal throughout the prostate. Very likely that the peripheral zone contained the highest levels of Ca, because this metal level in the peripheral zone is 34% higher than that in the whole gland volume.

4.5. VARIABLE DISTRIBUTION OF CA BETWEEN THE DIFFERENT COMPONENTS OF PROSTATIC TISSUE

According to Deering et al. [83], prostatic tissue contains three main components: glandular epithelium, prostatic fluid contained in the glandular lumina, and fibromuscular tissue or stroma. Studies on the Ca content in epithelium and stroma that was separated from each other were not found. However, the Ca concentrations in prostatic cells (both epithelial and stromal) have been investigated in Zaichick et al. study [17]. This level of prostatic intranuclear Ca is at least an order of magnitude higher than Ca concentrations in most other tissues of human body [17].

There are several publications on the Ca concentration in prostatic fluid [76-81]. The median of the means of these concentrations (802 mg/L) agrees well with the finding by Kavanagh et al. [79]. It was also found that Ca concentration in prostatic fluid does not depend on age.

4.6. DIETARY CA AND CA SUPPLEMENT INTAKE

Because significant correlations between high Ca intake and the risk of prostate cancer have been reported [30-33], it is possible hypothesized that dietary Ca and Ca supplement intakes affect the metal's levels in the prostate. There are data that support this hypothesis. For example, according to Tohno et al. [52] the mean Ca mass fraction in the Japanese prostates (1280 mg/kg wet tissue) was 1.7 times higher than in the Thai prostates (750 mg/kg wet tissue). Likely, the differences in dietary preferences of Thai and Japanese subjects may well explain this difference.

Thus, according our study no one influencing factor could

explain the variability of published means for prostatic Ca levels from 17 mg/kg to 1280 mg/kg in wet tissue. For example, the most powerful factor was age when it was found that the prostatic Ca level of boys before puberty was almost 2 times lower than that of males aged 14-30 years [12, 13]. However, the lowest mean level reported in literature (73 mg/kg wet tissue) was found in the prostate of subjects aged 16-37 years [45]. It is, therefore, reasonable to assume from data of our study that inaccuracy of analytical technologies employed caused so great variability of published means for prostatic Ca levels. This conclusion was supported the fact that the Certified Reference Materials for quality control of results were used only in a very few reported studies.

There are some limitations in our study, which need to be taken into consideration when interpreting the results of this review. The sample size of each study was sometimes relatively small (from 1 to 198), and a total of 1357 normal controls were investigated from all 36 studies. As such, it is hard to draw definite conclusions about the reference value of the Ca content in "normal" prostate as well as about the clinical value of the Ca levels in "normal" prostates as a biomarker.

5. CONCLUSIONS

The present study is a comprehensive study regarding the determination of Ca content in "normal" human prostates. With this knowledge Ca levels may then be considered as a biomarker for the recognition of prostate disorders. The study has demonstrated that levels of Ca in "normal" prostates depends on many factors such as age, androgen levels, zone of human prostate sampled, relative amounts of different types of prostatic tissue studied, dietary Ca, and Ca supplement intake. Because of the uncertainties we have outlined, we recommend other primary studies be performed.

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