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Review Article

Bismuth Level in the Prostate of the Normal Human: A Systematic Review

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ABSTRACT

Knowledge of the etiology and pathogenesis of most prostate malfunctions and pathologies is very limited. Despite advances in medicine, the differential diagnosis of benign hypertrophic and carcinogenic prostate has steadily increased in complexity and controversy. It has been suggested that the prostate bismuth (Bi) level may help solve these problems related to prostate disorders, especially as an indicator of prostate cancer risk, as an elevated Bi level in the prostate may be a sign of prostate cancer in the future. These suggestions promoted more detailed studies of the Bi level in the prostate of healthy men. In present review we analyze data published concerning Bi prostatic levels in healthy persons. In all 2249 items in the literature of the years dating back to 1921 were identified in the following databases: PubMed, Scopus, Web of Science, the Cochrane Library, 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 Bi content of normal prostates was evaluated. Of the articles examined, 15 were selected for objective analysis of data from 760 healthy subjects. The contents of prostatic Bi (on a wet mass basis) spanned the interval from 0.00066 mg/kg to ≤0.04 mg/kg with 0.0046 mg/kg as median for their means. The data included a wide range of values and the samples were small, hence it is advisable that further studies with strong quality control of results be performed.

Keywords: Bismuth, Human prostate gland, Normal prostatic tissue, Biomarkers

Abbreviations

Bi: Bismuth; PCa: Prostate cancer; BPH: Benign prostatic hyperplasia; TE: Trace element; AES: Atomic emission spectrometry; ICP-MS: Inductively coupled plasma mass spectrometry; ICP-OES: Inductively coupled plasma optical emission spectrometry; M: Mean; SD: Standard deviation; WHO: World Health Organization

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 biomedical advances, the differential diagnosis of prostate diseases 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.

In our previous studies the involvement of trace elements (TEs) in the function of the prostate gland was indicated. [4-15]. It was also found that content of TEs in prostatic tissue, including bismuth (Bi), can play a significant role in etiology of PCa [16-21]. Furthermore, it was demonstrated that the changes of some TE levels and Zn/Bi ratios in prostate tissue can be useful as biomarkers [22-28].

The first data of Bi content in human prostatic tissue (0.05 mg/kg of wet tissue) were published almost 60 years ago in the early 60s [29,39]. Zakutinsky [29] and Tipton and Cook [30] indicated that the content of Bi in the human prostate equals or below than 0.04 and 0.02 mg/kg of wet tissue, respectively. This finding allowed conclude that the prostate can accumulate Bi, because the level of metal in glands was almost four orders of magnitude higher the blood level (0.000002 mg/L) [31]. Moreover, recent experimental results identified that some Bi compounds

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should be considered as genotoxic carcinogens [32,33]. These findings promoted more extensive considerations of the Bi content of prostatic tissue of healthy persons, as well as of patients with different prostatic disorders, including BPH and PCa.

The effects of TEs, including Bi, are related to their level in tissues and fluids. 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 levels, and finally to toxic and even life-threatening concentrations [34-36]. In this context, until now there are no data on any biological function of Bi in organisms, but a lot of publications testify to adverse health effects in different organs or tissues of exposure to this metal and its compounds [37-42]. However, it still remains unclear what precise mechanism is responsible for Bi genotoxicity [32,33].

By now, a few publications have reported the level of Bi content in tissue of "normal" and affected glands. However, subsequent research works has been considered necessary to provide a practical reference data of Bi contents in prostate norm and disorders, because the findings of various investigations indicate some discrepancies.

The present study deals with the importance of Bi contents in prostate tissue as a biomarker of gland condition. Therefore, we systematically reviewed all relevant literature and performed a statistical analysis of the Bi level in "normal" gland tissue, which may provide insight into the etiology and diagnosis of prostate diseases as a higher Bi rate than these normal rates may be an indication of the possibility of pathological development in the prostate.

MATERIALS AND METHODS

Data Sources and Search Strategy

Aiming at finding the most relevant articles for this review, a thorough comprehensive web search was conducted by consulting the PubMed, Scopus, Web of Science, the Cochrane Library, and ELSEVIER-EMBASE databases, as well as from the personal archive of the author collected between 1966 to December 2020, using the key words: prostatic trace elements, prostatic Bi content, prostatic tissue, and their combinations. For example, the search terms for Bi content were: "Bi mass fraction", "Bi content", "Bi level", "prostatic tissue Bi" and "Bi of prostatic tissue". The language of the article was not restricted. The titles from the search results were evaluated closely and determined to be acceptable for potential inclusion criteria. Also, references from the selected articles were examined as further search tools. Relevant studies noted for each selected article were also evaluated for inclusion.

ELIGIBILITY CRITERIA

Inclusion Criteria

Only papers with quantitative data of Bi prostatic content were accepted for further evaluation. Studies were included if the control groups were healthy human males with no history or evidence of urological or other andrological disease and Bi levels were measured in samples of prostatic tissue.

Exclusion Criteria

Studies were excluded if they were case reports. Studies involving persons from Bi contaminated area and subjects that were Bi occupational exposed were also excluded.

DATA EXTRACTION

A standard extraction of data was applied, and the following available variables were extracted from each paper: method of Bi determination, number and ages of healthy persons, sample preparation, mean and median of Bi levels, standard deviations of mean, and range of Bi levels. Abstracts and complete articles were reviewed independently, and if the results were different, the texts were checked once again until the differences were resolved.

STATISTICAL ANALYSIS

Studies were combined based on means of Bi levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of Bi contents. The objective analysis was performed on data from the 15 studies, with 760 subjects.

RESULTS

Information about Bi 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 and PCa risk prognosis [28,34]. Thus, it dictates a need for reliable values of the Bi levels in the prostatic tissue of apparently healthy subjects, ranging from young adult males to elderly persons.

Possible publications relevant to the keywords were retrieved and screened. A total of 2249 publications were primarily obtained, of which 2234 irrelevant papers were excluded. Thus, 15 studies were ultimately selected according to eligibility criteria that investigated Bi levels in tissue of normal prostates **(Table 1)** and these 15 papers [9,13,14,27,29,30,43-51] comprised the material on which the review was based. A number of values for Bi 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% [52-55] and ash - 1% (on a wet mass basis) contents in normal prostates of adult men [30,54,56,57].

Table 1 summarizes general data from the 15 studies. The retrieved studies involved 760 subjects. The ages of subjects were available for 13 studies and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 14 studies. All fourteen studies determined Bi levels by destructive (require high temperature drying, ashing or acid digestion of tissue samples) analytical methods **(Table 1)**: one using atomic emission spectrometry (AES), and thirteen - inductively coupled plasma mass spectrometry (ICPMS).

Figure 1 illustrates the data set of Bi measurements in 15 studies during the period from 1962 to 2020.

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

Reference	Method	n	Age, range years	Sample preparation	Bi	
					M±SD	Range
Zakutinsky [29]	-	-	-	-	≤0.04 w	-
Tipton [30]	AES	50	Adult	D, A	≤0.02w	Max. 0.02
Zaichick [43]	ICP-MS	64	13-60	AD	0.0036±0.0082	0.00017-0.0425
Zaichick [9]	ICP-MS	16	20-30	AD	0.0031±0.0088	-
Zaichick [44]	ICP-MS	28	21-40	AD	0.00075±0.00041	0.00031-0.0020
		27	41-60	AD	0.0065±0.0109	0.00017-0.0425
		10	61-87	AD	0.0014±0.0013	0.00034-0.0033
Zaichick [13]	ICP-MS	50	0-30	AD	0.0036±0.0096	-
		29	0-13	AD	0.0062±0.0129	-
		21	14-30	AD	0.00078±0.00042	-
Zaichick [14]	ICP-MS	16	20-30	AD	0.00066±0.00029	-
Zaichick [45]	ICP-MS	65	21-87	AD	0.0034±0.0078	-
Zaichick [46]	ICP-MS	28	21-40	AD	0.00087±0.00069	-
		27	41-60	AD	0.00824±0.01772	-
		10	61-87	AD	0.00158±0.00174	-
		37	41-87	AD	0.00637±0.01533	-
		65	21-87	AD	0.0043±0.0102	-
Zaichick [47]	ICP-MS	32	44-87	AD	0.0046±0.0105	-
Zaichick [48]	ICP-MS	37	41-87	AD	0.0049±0.0112	-
Zaichick [27]	ICP-MS	37	41-87	AD	0.0049±0.0112	-
Zaichick [49]	ICP-MS	37	41-87	AD	0,0061±0,0120	0,00018-0,0467
Zaichick [50]	ICP-MS	37	41-87	AD	0.0049±0.0095	0.00017-

						0.0425
Zaichick [51]	ICP-MS	37	41-87	AD	0.0049±0.0095	0.00017-0.0425
Median of means				0.0046		
Range of means (M_{min} - M_{max})				0.00066 –≤ 0.04		
Ratio M_{max}/M_{min}				(0.04/0.00066) = 60.6		
All references				15		

M: arithmetic mean; SD: standard deviation of mean; AES: atomic emission spectrometry; ICPMS: inductively coupled plasma mass spectrometry; D: drying at high temperature; A: ashing; AD: acid digestion

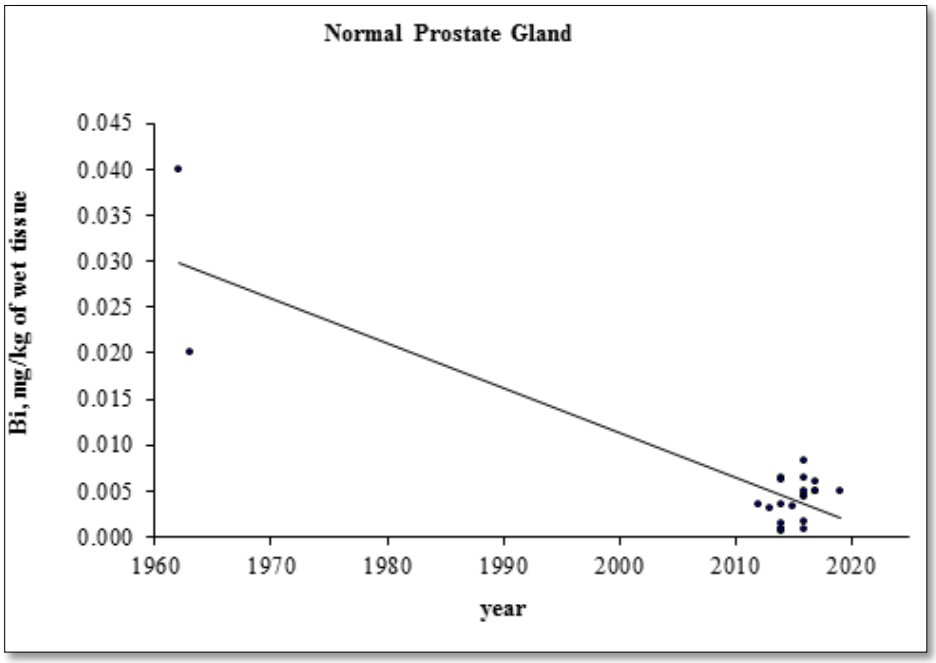

Figure 1. Data on Bi content in normal prostate tissue reported from 1962 to 2020 year.

DISCUSSION

The range of means of Bi mass fractions reported in the literature for "normal" prostatic tissue varies widely from 0.00066 mg/kg [14] to ≤0.04 mg/kg [29] with median of means 0.0046 mg/kg wet tissue **(Table 1)**. Thus, the maximal value of mean Bi mass fraction reported [29] was 60.6 times higher the minimal value of mean [14]. This variability of reported mean values can be explained by a dependence of Bi content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, possible non-homogeneous distribution of Bi levels throughout the prostate gland volume, age, ethnicity, diet, smoking, alcohol intake, consuming supplemental Zn and Se, 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 Bi content was measured in pieces of the prostate. Therefore, published data allowed us to estimate the effect of only a few factors on Bi content in "normal" prostate tissue.

ANALYTICAL METHOD

The trend line of Bi content data in "normal" prostate **(Figure 1)** showed that an improvement of analytical technologies during last almost 60 years impacted significantly on the means and variability of reported values. Thus, in our opinion, the leading cause of inter-observer

variability was insufficient quality control of results in studies published in the early 60s [29,30]. In all reported papers destructive analytical methods were used. These methods require drying, ashing or acid digestion of the samples at a high temperature. There is evidence that use of this treatment causes some quantities of TEs to be lost [34,58,59]. On the other hand, the Bi 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. It is possible to avoid these problems by using non-destructive methods, but up to now there are no analytical methods which allow quantify Bi content in "normal" prostate without ashing or acid digestion of the samples at a high temperature. It is, therefore, reasonable to conclude that the strong quality control of results is very important factor for using the Bi content in prostatic tissue as biomarkers.

AGE

In a few studies a significant increase in Bi content with increasing of age was shown by the comparison of different age groups or the Pearson's coefficient of correlation between age and Bi content in prostate tissue [44,46]. The most detailed investigations of age-dependence of prostatic Bi were done by Zaichick and Zaichick [46]. For example, a strongly pronounced tendency for an age-related increase of Bi mass fraction was observed in the prostate for the third to sixth decades [46]. In prostates of 41–60-year-old men, the mean Bi mass fraction was almost one order of magnitude higher than that in the prostates of 20–39-year-old males. Thus, the accumulated information, studied by us from reported data, allowed a conclusion that there is a significant increase in Bi mass fraction in "normal" prostate from age 21 years to the sixth decades.

ANDROGEN-INDEPENDENCE OF PROSTATIC BI LEVELS

There was not found any difference between Bi levels in prostates of teenagers before puberty and of post pubertal teenagers and young adults [9,13,14]. These findings allowed us to conclude that the Bi content in "normal" prostates does not depend on the level of androgens, and vice versa.

DIETARY BI INTAKE

Bi exposure occurs through various ways like food and water consumption, inhalation, and skin contact. Food and drinking water are the main sources of Bi exposure [60,61]. Most people receive the largest portion of their daily Bi intake via food and Bi is contained in all kinds of food. Data on Bi dietary intakes are very limited and vary widely from 0.0004 mg/day in the United Kingdom (UK) [60-63] to 1.58 mg/day in the Canary Islands [64]. In the UK study the highest contents of Bi was found in dairy products (0.0064 mg/kg), sugar (0.005 mg/kg), and milk (0.002 mg/kg) [62]. In the Canary Islands study the highest contents of Bi was found in viscera (38.1 mg/kg), while the lowest in yogurts (0.184 mg/kg). There were no found significant differences between Bi content in the different types of food including cold meat and sausages, red meat, milk, vegetables, potatoes, nuts, pastries, sweets, eggs, soft drinks, and alcoholic beverages [64]. In oils and waters Bi concentrations were under the detection limit (0.02 mg/L) of ICP-OES method used in the study [64]. In accord with this study the Bi concentration in milk (Spain, Burgos) was 0.305±0.426 mg/L (M, mean ± SD, standard deviation), while Bi content in the milk samples in Turkey was indicated at least one order of magnitude lower and ranged from 0.0065 to 0.0143 mg/L [65].

It was found that population dietary exposures in the UK have increased by 5-fold for 10 years [62]. In spite of this fact, till now there are no health-based guidance values for Bi dietary intake. Moreover, no data available on levels of Bi in drinking water in different countries, and a World Health Organization (WHO) drinking water guideline value has not been set [62].

It was shown that a strong link exists between Bi intake and this metal level in key organs, such liver and kidney [66]. From this it was hypothesized that dietary Bi intake affects the metal's levels in the prostate.

PROSTATIC BI CONTENT IN COMPARISON WITH OTHER BODY ORGANS, TISSUES AND FLUIDS

The determination of Bi in human organs, tissues and fluids is subject to large variation and older data should be approached with caution. In recent publication data on Bi content in human organs were not found, but the liver and kidney have been shown to be the target organs of Bi [39]. It is known also that the content of Bi in the kidney approximately one order of magnitude higher than in other organs (e.g., liver, lung, skeletal muscles, brain, bones) [67]. Reported concentrations of this metal in blood serum and urine of non-exposed persons varied very widely. For example, in old publications blood Bi levels were between 0.001 mg/L and 0.015±0.012 mg/L (M ± SD) [68], while in the study of Vanhoe [69] published in 1993 values of Bi concentrations in human serum of healthy adults (n=19) gave a range from <0.000007 to 0.00067 mg/L, which is almost two orders of magnitude lower than older data. The result reported by Vanhoe [69] is very similar to data obtained in recent investigation of Borbinha [42]. In this study reference value for normal Bi content in serum was estimated to be <0.0005 mg/L. In old articles Bi in urine non-exposed persons was reported as between 0.0082±0.0164 (M ± SD) and 0.022±0.020 (M ± SD) mg/L [68] but in accord with recent studies normal urine Bi concentration should be less than 0.001 mg/L [38,40,70].

Because the median of prostatic Bi content means obtained in the present review (0.0046 mg/kg of wet tissue) is approximately one order of magnitude higher the reference serum value (<0.0005 mg/L), it is reasonable to confirm that the prostate gland is also a target organ for this metal.

It is known that Bi is deposited in many organs [38], but is retained longest in the kidney [66]. The half-life of Bi in blood varies from 3.5 minutes to 17–22 years [39]. Thus, in spite of the possible changes in Bi intake, humans are in a state of positive Bi balance, because there is a component of Bi metabolism with very long half-life. This may well explain the increase of Bi content in kidney and some other key organs, including prostate, with the increase of age (see paragraph "Age").

Bi occurs naturally as a free metal or minerals, such as bismite (bismite oxide) and bismuthite (bismuth sulfide), which is commonly associated with sulfide ores of lead, copper and tin dioxide [70]. All-natural chemical elements of the Periodic System, including Bi, present in all subjects of biosphere [34,71,72]. During the long evolutional period intakes of Bi in organisms were more or less stable and organisms were adopted for such environmental conditions. Moreover, organisms, including human body, involved low doses of this metal in their functions [73].

The chemical behavior of Bi is similar to that of As, Pb, and Sb [76]. For centuries Bi minerals has been used in medicine and cosmetics, as well as pigments [39,70,74,75]. Since the 19th century Bi-contained compounds has been used in plenty of applications for the treatment of a wide range of diseases including syphilis, amebiasis, colitis, and other bacterial and parasite infections. However, Bi compounds use slowed down in the middle of the 20th century after the reversible Bi encephalopathy occurred in France and Australia [74]. For example, in France between 1973 and 1980 approximately 1000 cases of Bi related neurotoxicity and over 70 deaths were reported [74]. Thus, today Bi salts are primarily used for the treatment of peptic ulcers, functional dyspepsia, chronic gastritis, and other gastrointestinal disturbances [39].

In spite of a long story of Bi using in medicine and cosmetics, a really drastically increase of environmental Bi pollution links with the industrial revolution, with appearing various sources of this metal exposure. Bi has many important properties like softness, low-melting point, high relative density, resistance to corrosion, low thermal conductivity, and extreme diamagnetism. This metal and its compounds are widely used in non-ferrous metallurgy, as well as in arm, atomic, electronic, chemical, ceramic, pharmaceutical, and cosmetic industry, Bi compounds have a multitude of uses in industrial processes and products, such as the manufacture and reprocessing of nuclear fuel rods, battery cathodes, semiconductors, numerous readily fusible alloys, quenching baths for steel production, catalysts in the chemical industry, flame retardants, mirrors, as well as for anti- Helicobacter pylori therapy and dental health [41,70]. Bi is heavier and the relatively non-toxic metal in comparison with lead. As such, there is an increased use of Bi as a replacement for lead in manufacturing of lead-free shot bullets, malleable steels, lubricating greases, fire sprinkler systems, ceramic glazes, fishing sinkers, food processing equipment, free-machining brasses for plumbing applications, crystal ware, thermoelectric materials, solders, pearlescent pigments, cosmetics, medicines, etc. [70,75]. By now there are 39 Bi compounds, 17 of which are employed in the pharmaceutical industry and in many cosmetic products [76]. Furthermore, Bi in the nanomaterial forms has great potential for computed tomography imaging and thermotherapy [41,74,77].

Environmental Bi pollution occurs mainly through a combination of land (through atmospheric emissions originating from residues from coal, oil, and gas combustion, urban refuse, mine tailings and smelter slag, and also from waste, fertilizers and sludge application), water (through irrigation and industrial liquid waste), and air (through atmospheric industrial emissions and vehicle exhaust) contamination and is subsequently introduced into the food chain and drinking water [78-80]. In contrast to organic pollutants the non-biodegradable nature of Bi, as all other metals, is the prime reason for its prolonged persistence in the environment. Due to its non-biodegradable nature and continuous use, Bi concentration accumulates in the environment with increasing hazards [81]. Furthermore, in the environment, inorganic Bi can be bio transformed into highly mobile, membrane-permeable and therefore toxic trimethyl bismuth by methanobacteria [32,33]. Moreover, it was found that intestinal microbiota of human body exhibit highly productive mechanisms for the formation of this toxic volatile derivative trimethyl bismuth [82], which induces cyto- and genotoxic effects in human cells [32]. These findings should be considered in the medical application of Bi, as well as in environmental and occupational medicine, since the formation of methylated Bi derivatives in the human gut may damage mammalian cells, including cells of prostate.

Bi is an important product in the world industry. For example, the world production of Bi in 2017 was estimated to be about 17 thousand tons [83]. The world's largest producers are China and Laos. Other countries as Japan, Mexico, Kazakhstan, and Canada continue to increase this metal production [83]. Since the use of Ba is linked to the rapidly developing modern technologies, we can conclude that the need of industry in this metal increased for decades and would for continue to increase in the future. Age-dependent increase of Bi mass fractions in the 'normal" prostate tissue, which was indicated in the present review, indirectly confirm this conclusion. As was mentioned above, elevated Bi level is a poisonous factor affecting every organ in the body and the prostate gland is not the exclusion.

Thus, according our study for not polluted areas no one influencing factor could explain the variability of published means for prostatic Bi levels from 0.00066 mg/kg to ≤ 0.04 mg/kg of wet tissue. Moreover, prostate tissue Bi contents showed large variations among individuals (values ±SD for means in Table 1), but sources of the variation remain unknown. 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 Bi 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 10 to 65), and a total of 760 normal controls were investigated from all 15 studies. As such, it is hard to draw definite conclusions about the reference value of the Bi content in "normal" prostate as well as about the clinical value of the Bi levels in "normal" prostates as a biomarker.

CONCLUSION

The present study is a comprehensive study regarding the determination of Bi content in "normal" human prostates. With this knowledge Bi levels may then be considered as a biomarker for the recognition of prostate disorders. The study has demonstrated that level of Bi in "normal" prostates depends on many factors such as age, dietary Bi intake, and others. Because of the uncertainties we have outlined, we recommend other studies on Bi content in "normal" human prostate with the strong quality control of results be performed.

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