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(REVIEW ARTICLE)

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A systematic review of the cadmium content of the normal human prostate gland

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Abstract

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 cadmium (Cd) 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 Cd have been made. Here we analyze data published concerning Cd prostatic levels in healthy subjects. In all 1889 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. From the papers examined, 36 were selected for the objective analysis of data from their 1215 healthy patients. On a wet mass basis their prostatic Cd levels spanned the interval from 0.012 mg/kg to <0.76 mg/kg with 0.138 mg/kg as the median of their means. It is accepted that the prostatic Cd content is contingent on a wide variety of aspects of the host's milieu, including androgen levels, presence or absence of tobacco use, Cd content of food and drink, age, environmental levels of Cd and the method of analysis. The data encompassed a wide range of values and the sample was small, hence it is advisable that further studies be performed.

Keywords: Biomarkers; Cadmium; Human prostate; Normal prostatic tissue

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. 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.

We have previously shown that trace elements (TEs) can significantly affect prostatic function [4-15]. Also published results indicate that prostatic cadmium (Cd) and other TE content are important influences for the occurrence of PCa [16-20]. Further, the value of certain TE levels and the level ratio TE/Cd as biomarkers of prostate pathology has been established [21-28].

In 1956 very high levels of human prostatic Cd content were first recorded [29], when Koch et al. measured the levels of TEs, including Cd, in a wide variety of human tissues. In the four prostates they studied, mean Cd levels comprised about 10 mg/kg of ashed prostatic tissue. Smith et al. [30] in 1960 first determined that human prostates can store Cd,

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after discovering that men with occupational exposure to Cd had prostatic levels about two orders of magnitude higher than in the unexposed. After another study, performed 16 years later by Lemen et al. [31], the conclusion that occupational exposure to Cd increases the risk of prostate cancer in man was done by the International Agency for Research on Cancer (IARC) [32]. This relation between prostatic Cd levels and PCa prompted further comparative and comprehensive studies of prostatic levels. in both those not exposed and those exposed to Cd. Others, subject to various prostatic pathologies, including PCa and BPH, were also studied in terms of their Cd levels.

Cd and other TEs can affect prostatic function by means of their tissue concentrations. Levels can be lowered or raised and an excess of one TE can deleteriously influence the action of another TE. A sufficiently great excess can cause various states of dysfunction, even a life threatening situation [33]. It has been noted that the risk of human breast, colon, lung and prostate cancers is well correlated to the subject's previous exposure to Cd [34-36]. But the processes which facilitate such malignant changes remain unknown. Existing models for such transformation involve damaged DNA repair mechanisms, highly reactive oxygen species, inhibition of the pro-apoptotic function of caspase cascades, changing the Bcl2/Bax ratio and preventing p53 signalling. Any or all of these actions may participate in induction of PCa by excess Cd [37].

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

2. Material 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 PubMedthe 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 Cd content, prostatic tissue) in the years from 1966 to the present, was also used. As an example of the method employed, the search terms; "Cd content", "Cd level", "prostatic tissue Cd", "Cd mass fraction" and "Cd of prostatic tissue" were used to determine data to provide Cd 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

2.2.1. Inclusion criteria

For further evaluation of a paper, a necessary condition for acceptance was presentation of quantitative Cd 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 Cd levels were determined.

2.2.2. Exclusion criteria

All case reports were excluded, as were studies of subjects who were exposed to Cd, whether because of work related contact or residence in a region polluted by Cd.

2.3. 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 Cd content measurement, the ranges of Cd 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.

2.4. Statistical analysis

Studies were combined based on means of Cd levels in prostatic tissue. This analysis was done on data mined from 36 studies, including 1215 persons. The data divergence was analyzed using both their "range of means" and "median of means".

3. Results

Interest in the Cd content of prostates afflicted with various disorders stems from a possibly increased comprehension of both the pathogenesis and etiology of these disorders. Also it is expected to lead to improved diagnostic criteria, especially for PCa, and also evaluation of PCa's prognosis and risk factors [20,28]. This is the principal incentive to obtain dependable values for the Cd content of the prostates of males of all ages and in apparent good health.

In all 1889 studies were found and considered possibly able to contribute to this study. Their identification resulted from screening of keywords. Of them 1854 were eliminated from further consideration after application of the criteria described above. From the remaining 36 publications [9,13,14,26,29,30,38-67] useful Cd level data was extracted and comprises this review (Table 1). Among the data selected some mass fractions were obtained using a wet mass basis and others not. We used all these data with the following adjustment. Allowance was made for the difference between wet based and non-wet based prostatic tissue samples by inclusion for the latter; for water – 83% [68-71] and ash – 1% (assuming wet mass basis) as determined for normal adult male prostates [39,40,50,70]. The overall data from the 36 selected studies is given in Table 1.

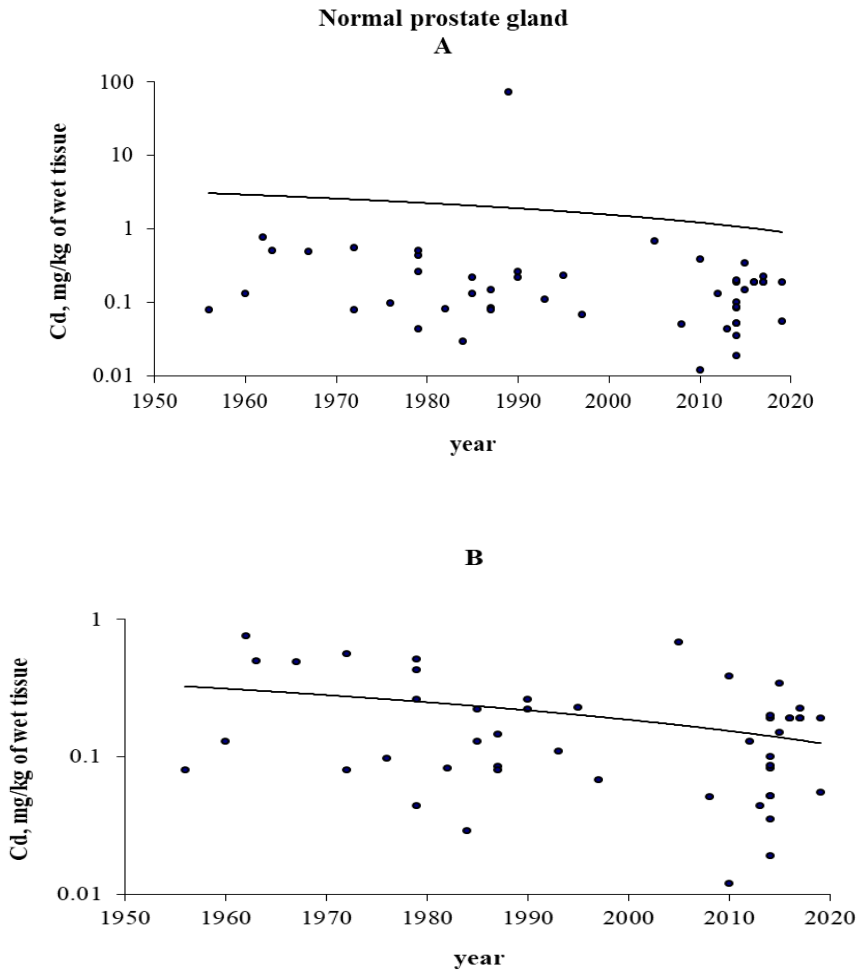

Figure 1 Data on Cd content in normal prostate tissue reported from 1956 to 2020 year with (A) and without (B) value 73.0 mg/kg wet tissue (1989 year).

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

Reference	**Method**	**n**	**Age, years M(Range)**	**Sample preparation**	**Cd**	
					Mean±SD	Range
Koch et al. 1956 [29]	AES	4	Adult	AD	0.08	-
Smith et al. 1960 [30]	AES	3	49-56	AD	0.13	0.085-0.15
Zakutinsky et al. 1962 [38]	-	-	-	-	<0.76	-
Tipton et al. 1963 [39]	AES	50	Adult	D, A	-	Max <0.5
Schroeder et al. 1967 [40]	AAS	50	Adult	A, AD	<0,49	-
Forssen 1972 [41]	XRF	12	Adult	A, AD	-	<0.08-0.56
Habib et al. 1976 [42]	AAS	9	36(25-58)	D, AD	0.097±0.012	0.041-0.177
Hienzsch et al 1979 [43]	AAS	110	<1-90	A, AD	0.044-0.51	-
	AAS	20	21-40	A, AD	0.26	-
	AAS	20	41-60	A, AD	0.43	-
Lathonen 1985 [44]	AAS	3	-	D, AD	0.22±0.03	0.20-0.26
	AAS	3	-	D, AD	0.13±0.04	0.10-0.18
Feustel et al. 1982 [45]	AAS	11	12-42	D, AD	0.082±0.007	-
Feustel et al. 1984 [46]	AAS	2	-	D, AD	0.029	-
Feustel et al. 1987 [47]	AAS	5	-	D, AD	0.085±0.044	-
	AAS	5	-	D, AD	0.080±0.051	-
	AAS	5	-	D, AD	0.146±0.094	-
Ogunlewe et al. 1989 [48]	AAS	55	Adult	AD	**73±85**	-
Lindegaard et al. 1990 [49]	AAS	5	61-76	F, AD	0.22±0.07	-
Saltzman et al. 1990 [50]	AAS	57	20-84	A, AD	0.26±0.11	-
Oldereid et al. 1993 [51]	AAS	41	40(18-80)	FF, AD	0.11	0.082-0.14
Borowiec et al. 1995 [52]	AAS	20	Adult	AD	0.23	-
Brys et al. 1997 [53]	AAS	11	Adult	AD	0.068±0.017	-
Galván-Bobadilla et al. 2005 [54]	AAS	1	65	AD	0.68	-
Sarafanov et al. 2008 [55]	ICPMS	15	Adult	AD	Median 0.051	0.034-0.19
Schöpfer et al. 2010 [56]	AAS	129	15-99	AD	0.012-0.384	-
Zaichick et al. 2012 [57]	ICPMS	64	13-60	AD	0.13±0.10	0.009-0.41
Zaichick et al., 2013 [9]	2 Methods	16	20-30	Intact, AD	0.044±0.044	-
Neslund-Dudas et al. 2014 [58]	ICPMS	21	Adult, NS	F, P, AD, NB	0.035	-
	ICPMS	25	Adult, ES	F, P, AD, NB	0.052	
Zaichick et al. 2014 [59]	2 Methods	28	21-40	Intact, AD	0.10±0.5	0.039-0.22
	2 Methods	27	41-60	Intact, AD	0.19±0.10	0.054-0.41
	2 Methods	10	61-87	Intact, AD	0.20±0.13	0.080-0.41

Zaichick et al., 2014 [13]	2 Methods	16	20-30	Intact, AD	0.083±0.046	-
Zaichick et al. 2014d [14]	2 Methods	50	0-30	Intact, AD	0.052±0.052	-
	2 Methods	29	0-13	Intact, AD	0.019±0.011	-
	2 Methods	21	14-30	Intact, AD	0.086±0.056	-
Zaichick et al. 2015 [60]	NAA	32	44-87	Intact	<0.34	-
Zaichick 2015 [61]	2 Methods	65	21-87	Intact, AD	0.15±0.10	-
Zaichick et al. 2016 [62]	2 Methods	32	44-87	Intact, AD	0.19±0.13	-
Zaichick et al., 2016 [63]	2 Methods	37	41-87	Intact, AD	0.19±0.13	-
Zaichick et al. 2017 [26]	2 Methods	37	41-87	Intact, AD	0.19±0.13	-
Zaichick et al. 2017 [64]	2 Methods	37	41-87	Intact, AD	0.225±0.129	0.056-0.525
Zaichick 2017 [65]	2 Methods	37	41-87	Intact, AD	0.19±0.11	0.054-0.41
Egger et al. 2019 [66]	ICPMS	1	66	AD	0,055	-
Zaichick et al. 2019 [67]	2 Methods	37	41-87	Intact, AD	0.19±0.11	0.054-0.41
Median of means		0.146 or 0.138 (without 73.0)				
Range of means (M_{min} - M_{max}),		0.012 – 73.0 or 0.012 – <0.76 (without 73.0)				
Ratio M_{max}/M_{min}		6083 or <63.3 (without 73.0)				
All references		36				

M – arithmetic mean, SD – standard deviation of mean, AES – atomic emission spectrometry, AAS – atomic absorption spectrophotometry, XRF– X-ray fluorescence, ICPMS – inductively coupled plasma mass spectrometry; NAA – neutron activation analysis, 2 Methods –NAA+ICPMS. NS – never-smokers, ES– ever-smokers, AD – acid digestion, D – drying at high temperature, A – ashing, F – fixed in ethanol/ chloroform/ formaldehyde, FF – defatted (fat free), P –paraffin embedded, NB – needle biopsy.

In 29 of these 36 studies where the patients' ages were provided, they ranged between 0 to 90 years. In 35 studies information about sample preparation and the analytical procedure was given. Of them 34 studies used destructive analytical methods to obtain Cd levels (high temperature drying, ashing, acid digestion, fixation in formaldehyde/chloroform/ethanol, resin/paraffin wax embedding, and tissue sample defatting). (Table 1) Fifteen studies employed atomic absorption spectrophotometry (AAS), 4 studies used inductively coupled plasma mass spectrometry (ICPMS), 3 atomic emission spectrometry (AES) and 1 X-ray fluorescence (XRF). In one study a nondestructive analytical method, such as {9} neutron activation analysis (NAA), was used exclusively. Eleven studies employed both destructive and nondestructive methods (ICPMS and NAA). In Figure 1 all Cd measurements from the 36 studies published in the interval 1956-2020, are presented.

4. Discussion

In 2016 a meta-analysis showed that there is a possible association between increased risk for PCa and raised levels of prostatic Cd levels [20]. This publication referred to only 6 studies which described normal prostatic Cd levels. Here we consider 36 relevant studies. In the literature describing tissue from "normal" prostates and their Cd mass fractions, they have a large variation. It ranges from 0.012 mg/kg [56] to 73.0 mg/kg [48] with median of means 0.146 mg/kg wet tissue (Table 1). The maximal value of mean Cd mass fraction reported [48] was 493 times higher than the median of Cd mass fraction means and at least two orders of magnitude higher than all other published means. We exclude the outlier value 73.0 mg/kg [48]. Even with deletion of this value there remains a broad range of mass fractions of Cd in normal prostates (0.012 mg/kg [56] to <0.76 [38] with median of means 0.138 mg/kg wet tissue and the Mmax/Mmin ratio about 60 (Table 1). There are many reasons for such a broad range. They include variations in age, diet, tobacco and alcohol use, total prostatic volume, the intake of Zn and Se, which are common dietary supplements, and ethnicity. Also there are imperfect methods of analysis, inconsistencies in the definition of a "normal" prostate and possible inhomogeneities in the Cd distribution within the prostate gland. In the studies cited these factors were not closely controlled. For some subjects an apparently healthy male suffering sudden death was presumed to have a "normal" prostate, yet without any viewing of his prostate to confirm its normality. A prostate was considered to be "normal" in other studies if it was non-cancerous, even if the tissue sample was located adjacent to a piece of malignant prostatic tissue. Prostates of subjects who died of acute and chronic non-prostatic illnesses, including some suffering from a

prolonged or a wasting disorder, were considered "normal" by the authors who published their Cd levels. Some studies had used whole prostates, others made measurements only on pieces. Therefore, in previously published results not all relevant factors were considered in the presentation of Cd levels of allegedly "normal" prostatic tissue.

4.1. Analytical method

In Figure 1 the trend line for Cd levels indicates that although analytical technology has much improved since 1957, the variation in reported mean values and spread of these "normal" prostatic levels is little changed. Hence we believe that the wide variation between reported Cd levels in the different studies results from unsatisfactory quality control. Also for the many reports which used AES, AAS and ICP-MS, or other such destructive analytical methods, it has been reported that they can result in loss of some TEs [33,72,73]. This is because these methods require the tissue samples to be subject to high temperatures for acid digestion. Another consideration is that the chemical agents required for acid digestion can contaminate the prostatic tissue with TEs. Where possible, compensation for all these factors should be made. In addition when tissue is fixed and embedded in paraffin/epoxy, there can be a loss of Cd when the tissue is fixed with formaldehyde/chloroform/ethanol. These setbacks may be averted if non-destructive methods are used. However currently to determine Cd levels in "normal" prostatic tissues, acid digestion at high temperature is necessary. An indubitable conclusion from this discussion is that quality control is of crucial importance if the Cd content of prostatic tissue is to be used as a reliable biomarker.

4.2. Age

Some studies showed that as the subjects' ages increased, their prostatic Cd levels did likewise. A Pearson's coefficient of correlation between them indicate this was significant [14,43,51,56,59]. The most detailed such correlation were those of Zaichick and Zaichick [14,59]. This was most evident from the 3rd to 6th decades [59] and the increase in Cd content was exponential. For men aged 41-60, mean prostatic Cd mass fraction was double that of males aged 21-40. These results were similar to earlier reports [43,56]. In 1979 Heinzsch et al. [43] found that the total "normal" prostatic Cd content increased after the age of 40 years, compared to levels in 21-40 males, by factors of 1.2 to 1.9. Further, Oldereid et al. 1993 [51] showed the mean Cd mass fractions in the prostates of 60 year old males was ≈3x that of 20 year olds. In 2010 Schöpfer et al. [56] studied smokers and non-smokers aged 60 and determined they had prostatic Cd mass fractions 3x that of those aged 20 years. From these data we conclude Cd mass fractions in "normal" prostates increase exponentially between the age of 21 and the 6th decade and this change is significant. Then, from the 6th to the 9th decade they remain approximately unchanged.

4.3. Androgen-dependence of prostatic Cd levels

There is a large increase in prostatic Cd content after puberty and it is close to an order of magnitude. Hence this increase, and Cd levels in general, are presumably controlled to a very great extent by androgens [14,43]. It is known there is an androgen-like action of Cd in prostatic epithelial cells [74]. So there may be a two directional interaction between the levels of both androgens and Cd in the "normal" prostate, yet no studies relevant to this hypothesis have been found.

4.4. Variable distribution of Cd between the different components of prostatic tissue

The Cd levels in "normal" prostatic epithelial and stroma, which had been separated from other tissue, have been determined [44,47]. Lathonen determined the former's Cd mass fraction was 1.7x that of the stroma [44], but Feustel et al. [47] could not detect any difference in these tissues' Cd content. Deering et al. [75] state that prostates contain three principal tissues; stroma or fibromuscular tissue, glandular epithelium and prostatic fluid within the glandular lumina. Clearly in studies of prostatic tissues some prostatic fluid could be lost when epithelium and stroma are separated. Now prostatic Zn is located mainly in the prostatic fluid (with about 3-5x greater concentration than in prostate solid tissue [76-81]). So the principal reservoir of prostatic Zn is in the prostatic fluid residing in the glandular lumina [5,10-15,17,18]. Cd and Zn have similar chemical properties [82]. Because of their similar chemical properties, prostatic fluid Cd levels should contain larger amounts of Cd than prostatic epithelial and stromal tissues. One paper deals with the Cd level in prostatic fluid and indicates it is 0.146 mg/L [83]. Yet this value closely approximates one result of the present work, for the Cd content of prostate tissue, which is 0.138 mg/kg for wet tissue.

4.5. Dietary Cd intake

Compared to many other TEs, Cd transfers more rapidly from soil to plant tissues and some species of plant can concentrate large amounts of this element, even when in soils containing small quantities of Cd [84]. For nonsmokers in unpolluted regions the intake of Cd is dietary and about 30mg daily [85]. Of this only about 1-3 mg is absorbed from the gut [85]. The body's Cd is found in many sites and its levels are similar in the prostate and in many other tissues

and organs [66]. However about 50% of the total body store of Cd is renal and hepatic [86]. But in polluted environments prostatic Cd levels are increased and can be up to about 100x the usual values [87]. It therefore seems likely that prostatic Cd content depends on dietary intake of Cd and this idea is indirectly supported by prostate data from smokers and nonsmokers, for tobacco smoke contains much Cd.

4.6. Smoking

Tobacco smoke differs greatly from food in that its Cd content is much more readily absorbed by the human body. On smoking about 50% of the Cd in inhaled smoke is absorbed directly into the pulmonary circulation, in great contrast to Cd in food, which is absorbed very poorly [85]. So smoking is an important source of Cd intake and smokers can absorb 2-3 mg of Cd daily, a quantity similar to the total intake from dietary sources [85]. The prostates of smokers have about twice as high a Cd content as nonsmokers for all their adult lives, Schöpfer et al. 2010 [56]. Neslund-Dudas et al. studied the prostatic Cd levels of smokers who suffered from PCa, in both the tumors and in nearby non-neoplastic prostate tissue, using ICP-MS [58]. Of their subjects 21 were nonsmokers and 25 smoked regularly. Both groups had similar ages, PSA (prostatic specific antigen) levels, Gleason grade at the time of diagnosis of PCa, dietary intake of Zn and estimated exposure to all metals, from occupational and all other sources. Those smoking at the time of the Cd determinations had Cd levels in their non-neoplastic tissue samples (adjacent to cancerous tissue) which were 1.5x those of the nonsmokers. This finding confirms the Cd level of a "normal" prostate strongly reflects the subject's smoking status.

All chemical elements of the Periodic Table are present in the biosphere [33,88,89]. Throughout evolution, the uptake of Cd by organisms has remained approximately constant. Organisms' adaptation has reflected both physiological needs and environmental conditions. Humans, and all other organisms, have always needed small quantities of Cd [90,91]. The earth's environment has changed significantly since the onset of the Industrial age, especially during the past century. Cd was discovered at the start of the 19th century and the application of Cd compounds in many industrial processes steadily increased. By the end of that century Cd was an important industrial component [92]. It is principally obtained as a byproduct of ores containing Zn, Pb, and Cu. The industrial applications of Cd are very numerous, including: constituents in the manufacture of plastics, ceramics, glasses, batteries, fungicides and fertilisers [84,85,93].

There is now significant pollution of Cd in land, water and the atmosphere. The sources are fuel burning (oil, gas and coal), vehicular emissions, waste from urban residents, fertilisers, mining, smelting and other industrial processes. All this contaminates water supplies and finally Cd enters the food chain. Production of Cd from 1997 to 2004 was near constant in the USA and Europe. In contrast Asiatic Cd production steadily increased by 43% and it is now near to 60% of the world's Cd burden [93]. Rapidly advancing technology involves much Cd use. Such use has increased significantly in the past and this trend seems highly likely to persist.

These environmental changes during the last century have resulted in an increase in the human burden of Cd [84,94], which will probably continue. Evidence for this trend is seen in age dependent increasing Cd levels in "normal" prostates. Such changes are much closer to exponential than to other increases [14,59].

This study indicates that there are several factors which contribute to the variation of reported means of prostatic Cd content (0. 012 mg/kg to <0.76 mg/kg in wet tissue). One significant contribution to prostatic Cd level variation is age, as has been described above. Overall this work's data shows that the analytical methods used have contributed a large variation in values of prostate tissue Cd content. This assertion has confirmation from the fact that there was very little reported use of any Certified Reference Materials in others' analyses.

Our study has some limitations, which have to be considered to aid understanding of our review's results and conclusions. Some of studies contained few subjects and totals of groups ranged from 1 to 129 persons, although the sample size of normal controls totaled 1215 in all 36 studies. Such limitations make it difficult to make definitive conclusions about reference values of the "normal" prostates' Cd level. Thus further work is required before Cd content can be used as a reliable biomarker.

5. Conclusion

This work is a comprehensive study of the Cd content in "normal" human prostatic tissue. Knowing such Cd levels with sufficient precision can allow its use as a biomarker for the recognition of prostate disorders, especially PCa. The study has demonstrated that these Cd levels in "normal" prostates depend on many factors such as age, androgen levels, dietary and other Cd intake, particularly smoking. We have outlined current uncertainties, hence, we recommend other primary studies be performed before Cd levels can become reliable biomarkers.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

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