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Cadmium Levels in Tissue and Plasma as a Risk Factor for Prostate Carcinoma: a Meta-Analysis

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Abstract Cadmium is a heavy metal that has been suggested to be a carcinogen by evidence. A number of published studies have investigated the association between cadmium levels and prostate cancer, but the results were inconsistent. Thus, we conducted a meta-analysis to get a precise estimate of this subject. After a careful searching and screening, a total of 11 publications containing 14 separated studies were included. Based on a random-effect model, the pooled data showed that cadmium levels of prostate tissues (standard mean difference (SMD)=3.17, 95 % confidence interval (CI)=0.60–5.74, $P<0.05$) and plasma (SMD=4.07, 95 % CI=2.01–6.13, $P<0.05$) were significantly higher in prostate cancer patients than those in the healthy controls. No difference of hair and nail cadmium levels between the prostate cancer cases and the controls was found. The data suggested that cadmium exposure might exert an influence on the tumorigenesis of prostate tissues. Future investigations with large sample sizes are needed to verify the results.

Keywords Cadmium · Levels · Prostate carcinoma · Risk · Meta-analysis

Statement: This study is an original work

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Introduction

Prostate cancer is the most common cancer that is the sixth cause of cancer death in men in the world [1]. However, its risk factors remain unclear. Previously, epidemic factors such as smoking and alcohol consumption are believed to be risk factors for prostate cancer [2]. Besides, sexually transmitted infections [1], genetic variations [3], and even excess fatness [4] might also confer prostate cancer risk. Recently, dietary factors have been suggested to play a role in the genesis of prostate carcinoma [5]. For example, low-carbohydrate intake, soy protein, omega-3 (w-3) fat, green teas, tomatoes and tomato products, and zyflamend might reduce prostate cancer risk, and conversely, a higher saturated fat intake or a higher β-carotene status might increase carcinoma risk [6]. As we know, the dietary factors may influence the levels of trace elements such as selenium, zinc, arsenic, cadmium, and nickel in tissues or serums, which might exert an effect on cancer risk [7].

For prostate cancer, recent meta-analyses revealed that decreased zinc levels in prostate tissue may have an association with increased cancer risk [8]. Besides, increasing plasma/serum selenium may be related to a decreased prostate cancer risk [9]. Nevertheless, few meta-analyses on the association between other element levels and prostate carcinoma have been published.

Cadmium is a human neoplastic heavy metal that is usually taken up from vegetables and grains developed in contaminated soil. Once absorbed, it can bind to metallothionein and is stored in the tissues of solid organs such as kidney because the mechanisms for the excretion of this heavy metal from the body are absent [10]. The long biological half-life of cadmium in humans could lead to malignant transformation of tissues via multiple pathways [11]. Thus, cadmium accumulation in the body is thought to have a correlation with risk of a variety

of cancers, such as bladder cancer [12], pancreatic cancer [13], and lung cancer [14].

A number of studies have been devoted to the cadmium levels and prostate cancer risk. However, the results were inconsistent and conflicting. To our knowledge, few meta-analyses on this topic have been published to date. Thus, in the present study, we aimed to conduct a quantitative meta-analysis containing published data up to Sep. 2015 that increased statistical power to obtain a conclusive estimation.

Materials and Methods

Literature Search Strategy

A systematic search was carried out in multiple bibliographic databases such as Medline, EMBASE, and China National Knowledge Infrastructure (CNKI) without a language limitation, including all papers published up to Sep. 2015. In the initial search, a combination of the following keywords was used: *cadmium*, *trace element*, *neoplasm*, *tumor*, *cancer*, *prostate*, and *urinary system*. Other possible publications were screened by checking the references of the retrieved papers.

Inclusion Criteria

The following criteria were used for the literature selection: first, studies focused on the levels of cadmium in the bodies of patients with prostate carcinoma; second, papers must offer both exposed group and control group; and third, studies must offer the size of sample, the mean, and standard deviation (SD) of cadmium level or necessary information that readers can infer the results. Accordingly, the exclusion criteria were used as follows: first, papers showed insufficient information about cadmium levels; second, studies only concerned animal experiments or cell line cultures; and third, reviews or duplicate publications. After rigorous searching, we reviewed all papers according to the criteria mentioned above for further analysis.

Data Extraction and Quality Assessment

Eligible publications were independently reviewed by two of the authors according to the inclusion criteria. Data were extracted and illustrated in a database. For discrepancies of the data, a discussion was made in order to reach an agreement. On the basis of this situation, if a conflicting evaluation still existed, another author was consulted to resolve the dispute and then a final decision was made by the majority of the votes.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies, which ranges from 0 to 9 stars [15]. Studies with less than 4 stars were excluded.

Statistical Analysis

The SMDs and the corresponding 95 % CIs were used to compare the cadmium levels between patients with prostate carcinoma and controls. Heterogeneity testing was evaluated with a chi-square-based Q statistic test. If a P value for a given Q test was found to be more than 0.1, ORs were pooled according to a fixed-effect model (Mantel-Haenszel) [16]. Otherwise, a random-effect model (DerSimonian and Laird) was selected [17]. A funnel plot was constructed to assess the publication bias via visual inspection of the plot [18]. An asymmetrical plot indicated possible publication bias. Then, Egger's linear regression test was used to further evaluate symmetry of the funnel plot [19]. Statistical analysis was carried out using the program STATA 11.0 software (Stata Corporation, TX, USA).

Results

Study Characteristics

Possible publications relevant to the keywords were retrieved and screened. A total of 241 publications were primarily obtained, of which 212 irrelevant papers were excluded. Thus, 29 publications were eligible. After a careful review of the paper contents, three review articles [20–22] and four studies without healthy control group [23–26] were excluded. Then, 11 publications providing insufficient information [27–37] were further excluded. Lastly, 11 publications including 14 separated studies were selected for data extraction [38–47] (Fig. 1).

The NOS scores of all studies were greater than four, and thus, they were all included. Among the selected publications, only two was written in Chinese [38, 48], while the remaining nine were in English. The relevant information was listed in Table 1. As shown in this table, the first author and the number of cases and controls for each study were presented. The mean levels of cadmium and their standard deviations as well as other necessary information such as detection method and countries were also included. There were six studies that focused on prostate tissue, four on plasma, two on hair, and two on nail. A total of three methods for detecting cadmium levels were used, namely, flame atomic absorption spectrophotometry (AAS), flameless AAS, and graphite furnace AAS.

Meta-Analysis Results

Main results of the meta-analysis were shown in Table 2. The overall data from 14 studies were pooled in a random-effect model because significant heterogeneity was found among the studies (Q=619.71, P<0.05). The comparison of cadmium levels between prostate cancer cases and healthy controls

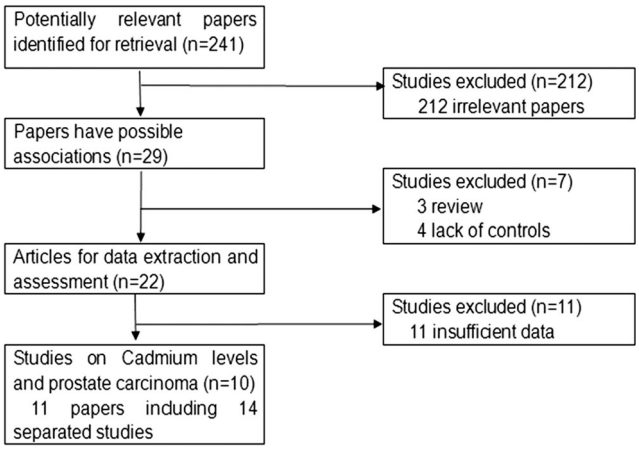

Fig. 1 The flow diagram of included/excluded studies

showed that cadmium levels in prostate cancer patients were markedly higher than those in the controls (SMD=3.19, 95 % CI=1.94–4.45, $P<0.05$).

When the data were stratified by sample types, significant differences were observed in the subgroups regarding prostate tissue (SMD=3.17, 95 % CI=0.60–5.74, $P<0.05$) and plasma (SMD=4.07, 95 % CI=2.01–6.13, $P<0.05$), demonstrating that levels of cadmium in prostate tissue and plasma are higher in prostate cancer cases than those in the controls, respectively. No difference could be found in the subgroups regarding hair (SMD=2.38, 95 % CI=−2.18–6.95, $P>0.05$) and nail (SMD=3.16, 95 % CI=−3.09–9.40, $P>0.05$), respectively (Fig. 2).

In the subgroup analysis about geographical location, significant differences were also shown in all groups except the Africa group (SMD=30.19, 95 % CI=−4.02–64.40, $P>0.05$). As shown in Table 1, there were a total of ten studies that provided information about the mean age for the cases and controls, and thus, these studies were stratified by age. Since the mean ages of the cases ranged from 55.18 to 73.0 years, the studies were divided into two subgroups, namely, less than 65 years (<65) group and equal to or greater than 65 years (≧65) group, respectively. The results showed that the significance of the two subgroups (≧65 SMD=4.42, 95 % CI=2.29–6.55, $P<0.05$; <65 SMD=4.00, 95 % CI=2.34–5.65, $P<0.05$) were in accordance with the overall data, respectively, as presented in Table 2 and Fig. 3.

Sensitivity analysis was used to evaluate the effect of a single study on the overall effect estimate by deleting any one study each time during repeated analysis. The results showed that the statistical significance of the results was not altered when any single study was omitted (data not shown), indicating the robustness of the results.

Bias Diagnostics

A funnel plot was created to detect possible publication bias. Then, Egger's linear regression tests were performed to assess the symmetry of the plot. A potential publication bias might

Table 1 Characteristics of studies included in the present meta-analysis

First author	Year	Sample size		Cadmium (Mean±SD)		Unit	Mean age (year)		Method	Samples	Country
		PC	Control	PC	Control		PC	Control			
Habib	1976	9	9	129.79±22.22	5.15±0.62	nmol/g	73.0	36.0	Flame AAS	Prostate tissue	Finland
Feustel	1982	33	11	1.62±0.96	0.48±0.24	μg/g	NA	NA	Flameless AAS	Prostate tissue	Germany
Lahtonen	1985	3	3	4.83±0.72	7.02±1.20	nmol/g	NA	NA	Graphite furnace AAS	Prostate tissue	Finland
Feustel	1986	17	45	8.12±4.41	7.78±4.05	ng/ml	71.0	47.3	Flameless AAS	Plasma	Germany
Feustel	1987	7	5	0.70±0.17	0.50±0.26	μg/g	NA	NA	Graphite furnace AAS	Prostate tissue	Germany
Ogunlewe	1989	12	55	24.2±0.9	15.2±0.6	μmol/l	67.3	61.2	Flame AAS	Plasma	Nigeria
Ogunlewe	1989	10	10	28.9±0.37	3.8±0.63	μmol/g	67.3	61.2	Flame AAS	Prostate tissue	Nigeria
Brys	1997	7	11	0.73±0.12	0.40±0.10	μg/g	NA	NA	Graphite furnace AAS	Prostate tissue	Poland
Ouyang	2000	18	10	0.19±0.22	0.18±0.15	μg/g	65.2	61.2	Graphite furnace AAS	Hair	China
Platz	2002	115	227	152.7±346.7	157.2±334.7	ppb	66.1	66.0	Graphite furnace AAS	Nail	USA
Qayyum	2014	74	66	1.084±0.107	0.774±0.096	μg/g	56.77	47.76	Flame AAS	Plasma	Pakistan
Qayyum	2014	67	67	1.629±0.159	1.021±0.090	μg/g	56.01	47.13	Flame AAS	Hair	Pakistan
Qayyum	2014	60	60	5.655±0.497	3.063±0.292	μg/g	55.18	46.58	Flame AAS	Nail	Pakistan
Chen	2015	85	90	13.58±3.64	7.45±2.31	μg/dl	64.7	65.9	Flameless AAS	Plasma	China

PC prostate carcinoma, *AAS* atomic absorption spectrophotometry, *NA* not available

Table 2 Main results of the meta-analysis

Factors	Overall SMD (95 % CI)	*z*	*P* value	Heterogeneity test		Number of studies	Model
				Q	*P*		
Total (PC vs control)	3.19 (1.94, 4.45)	4.99	<0.05	619.71	<0.10	14	Random-effect
Stratification by sample type							
Tissue	3.17 (0.60, 5.74)	2.41	<0.05	68.83	<0.10	6	Random-effect
Plasma	4.07 (2.01, 6.13)	3.87	<0.05	151.12	<0.10	4	Random-effect
Hair	2.38 (−2.18, 6.95)	1.02	>0.05	80.48	<0.10	2	Random-effect
Nail	3.16 (−3.09, 9.40)	0.99	>0.05	186.46	<0.10	2	Random-effect
Stratification by geographical location							
Europe and America	1.17 (0.18, 2.16)	2.31	<0.05	61.70	<0.10	7	Random-effect
Africa	30.19 (−4.02, 64.40)	1.73	>0.05	18.16	<0.10	2	Random-effect
Asian	3.22 (1.58, 4.86)	3.74	<0.05	160.66	<0.10	5	Random-effect
Stratification by age							
≧65	4.42 (2.29, 6.55)	4.07	<0.05	184.21	<0.10	6	Random-effect
<65	4.00 (2.34, 5.65)	4.74	<0.05	107.97	<0.10	4	Random-effect

PC prostate cancer patients, *SMD* standard mean difference

exist because Egger's test suggested that the funnel plot was not symmetrical (t=2.47, P=0.03).

Discussion

In the present study, we compared the levels of cadmium in the bodies between prostate cancer patients and healthy controls by performing a meta-analysis and found that cadmium levels in prostate tissues and plasma of prostate cancer patients were significantly higher than those of healthy controls, respectively, indicating that cadmium accumulation in prostate tissue and plasma might be involved in the neoplastic process of prostate tissues.

As a heavy metal, cadmium has been suggested to be a pathogenic factor or a carcinogen for humans by several

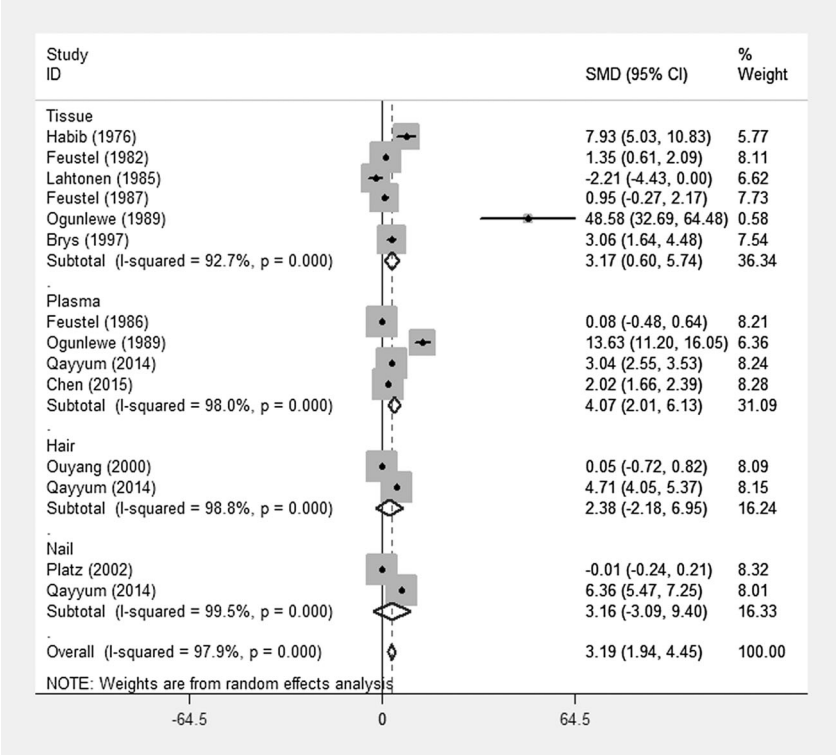

Fig. 2 The association of prostate cancer risk with cadmium levels (prostate cancer cases versus controls; stratified by sample type). Forest plots showed that cadmium levels of prostate tissues and plasma in prostate cancer cases were higher than those in the controls. No differences were found in the comparisons regarding hair and nail

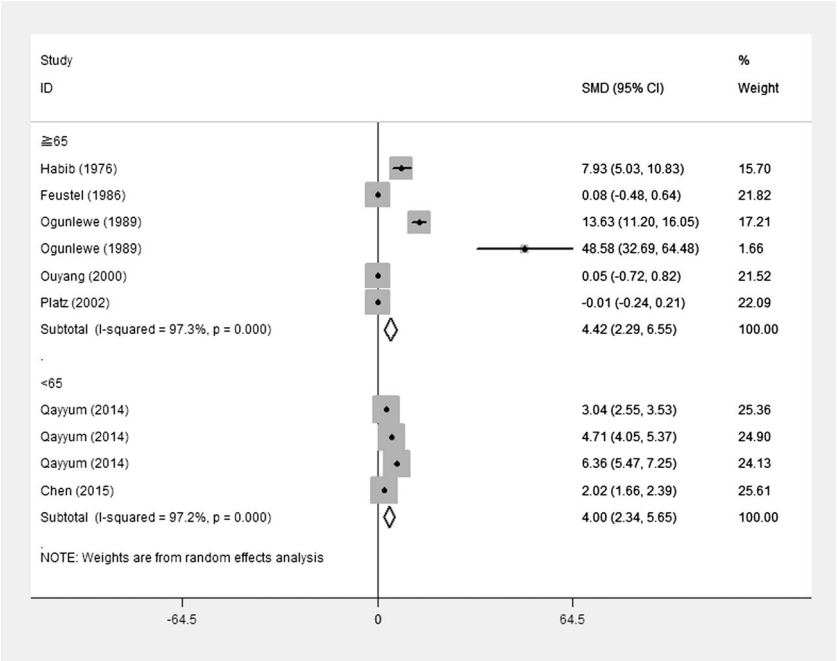

Fig. 3 The association of prostate cancer risk with cadmium levels (prostate cancer cases versus controls; stratified by age). Forest plots showed that cadmium levels in prostate cancer cases of were not higher or lower than those in the controls for the two subgroups

published meta-analyses. For instance, cadmium accumulation is responsible for hypertension, atherosclerosis, and acute coronary events [49]. Also, cadmium might influence the neurodevelopment and behavioral disorders in children [50]. Only a few meta-analyses reported the association of cadmium and cancer risk. In 2000, a meta-analysis showed that high exposure to cadmium may increase risk of pancreatic cancer [51]. Also, elevated levels of cadmium were found in breast cancer patients compared with those in the controls [52]. Nevertheless, environmental cadmium exposure at a low-level might be a risk factor for lung carcinoma [53]. Moreover, Larsson et al. suggested that cadmium, even at a low concentration, could increase mortality caused by cancer or non-cancer diseases [54]. The evidence supported the notion that cadmium exposure might be a pathogenic factor in a number of malignant disorders.

The underlying mechanisms by which cadmium initiates or assists cancerigenesis are not fully understood. Reports showed that exposure to cadmium at a low concentration could lead to DNA fragmentation [55] and microsatellite instability [56] in cells. Moreover, cadmium exposure could induce the secretion of tumor necrosis factor-alpha [57] that is a cytokine associated with a number of cancer risk [58]. Additionally, cadmium induces increase in reactive oxygen species formation, which in turn interferes with cell signaling and lastly induce DNA damage [59]. Thus, cancerigenesis of prostate tissues might be initiated. Notably, the cadmium levels in hair and nail between prostate cancer patients and controls are not significantly different. The data indicated a tendency that cadmium accumulated in organs and blood rather than skin appendages, consistent with a study by Bibi et al. [60] in which cadmium levels in hair and nail were low, though those in blood were high. Therefore, the skin appendages should be cautiously used to predict internal cadmium concentration [61].

As we know, cadmium might have a long half-life in the body owing to the absence of the mechanisms by which cadmium would be excreted out. Thus, the age and the cadmium concentration might be positively correlated. To address this topic, we conducted subgroup analysis on age. The data suggested that the age might not exert a marked influence on the overall results. However, in the present meta-analysis, all cancer cases with available mean ages were late-middle and aged men, while the controls were not well matched to the cases. Moreover, the mean ages of the cases and the controls were provided only in 10 out of 14 studies. Thus, the results should be interpreted with care. Future primary investigations covering wide age ranges are warranted to address this subject.

Significant heterogeneity was seen for the overall data, and thus, a random-effect model was used. We tried to stratify the data according to sample types and geographical locations, and however, heterogeneity still existed in each comparison, indicating that multiple factors such as study design, sample size, and lifestyle factors might lead to the heterogeneity. Nevertheless, sensitivity analysis suggested the robustness of the results. In the present study, evident publication bias was also shown for the overall data. However, it is worth noting that the number of the included studies was limited, which might result in the inaccuracy of the bias tests. On the basis of this situation, future well-designed studies comprising larger sample sizes are required to derive a precise estimate.

Several limitations might be included in this study. First, this study only involved data from articles published in Chinese and English. Thus, papers written in other languages were inevitably missed, and any selection bias must exist. Second, confounding factors, such as gender, smoking, and drinking, were not assessed in most of the included studies. Hence, it is difficult for us to conduct subgroup analyses on these factors, and the estimate for the comparison might deviate from the exactness. Third, the stages of prostate cancer were not considered and evaluated in most of the selected studies. Future investigations on this issue might help clarify the effect of cadmium on prostate cancer development.

In conclusion, the data of the present meta-analysis showed that cadmium levels in prostate tissues and plasma of prostate cancer patients were significantly higher than those of healthy controls, suggesting that cadmium exposure might exert an influence on the tumorigenesis of prostate tissues. Future investigations with large sample sizes are needed to verify the results.

Compliance with Ethical Standard

Competing Interests The authors declared that they have no competing interests.

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