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Review Article

Investigating the Relationship between Cadmium Exposure and the Risk of Prostate Cancer: A Systematic Review and Dose-Response Meta-Analysis

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Abstract

Background: Cadmium, a toxic heavy metal, experienced a surge in production during the 20th century due to the rise of nickel-cadmium batteries, metal plating, and plastic stabilizers. Exposure to cadmium primarily occurs through the consumption of contaminated food, such as vegetables and grains, as well as drinking water or inhaling polluted air. The objective of this study was to investigate the relationship between cadmium exposure and the incidence of prostate cancer using a systematic review and meta-analysis approach.

Methods: This research involved searching and retrieving observational and experimental studies conducted until May 2022 from various databases, including ISI Web of Science, Cochrane, Science Direct, Scopus, PubMed, and Google Scholar. Data analysis was performed using Stata 15 statistical software.

Results: The initial search yielded 794 articles, which were subsequently reduced to 427 articles after eliminating duplicates. Following the application of inclusion and exclusion criteria, a total of 16 studies were included in the meta-analysis. The odds ratio of prostate cancer compared to the first quartile of exposure in the second quartile was 1.03 (0.95-1.12), in the third quartile it was 1.12 (0.99-1.26) and in the fourth quartile of exposure was equal to 1.16 (0.79-1.70). Regarding the investigation of the probability of the occurrence of publication bias, the results of Begg's and Egger's tests were not statistically significant.

Conclusion: Although exposure to cadmium leads to an increase in the chance of prostate cancer, this chance increase was not statistically significant.

Keywords: Cadmium; Prostate cancer; Systematic review; Dose-response meta-analysis

Introduction

Heavy metals encompass a group of stable and non-biodegradable pollutants that infiltrate the food chain through water, soil, and air pathways (1). Their extensive utilization in various industries, households, agriculture, and medicine has resulted in their widespread release into the envi-

ronment, raising concerns about their potential detrimental effects on human health and the ecosystem (2, 3). The toxicity of these heavy metals is influenced by several factors, including the quantity and mode of exposure, chemical forms, and individual characteristics such as age, gender, genetics, and nutritional status (4, 5). Elements such as arsenic, cadmium, nickel, chromium, lead and mercury are more preferable in the field of public health due to their high toxicity (6).

Cadmium, a toxic metal belonging to the twelfth group and fifth period of the periodic table, poses significant health risks (7). Smoking, tobacco use, and a diet comprising cereals, potatoes, and vegetables are the primary sources of human exposure to cadmium, as it is absorbed from the soil (8). Occupational exposure occurs in industries such as metal plating, welding, chemical fertilizer manufacturing, insecticide production, nickel-cadmium battery manufacturing, nuclear fission units, and tetraethyl lead manufacturing (9). Additionally, cadmium is a byproduct of extracting metals like lead, zinc, and copper. The element is primarily absorbed through the respiratory system, digestive system, and skin. Once inside the body, cadmium is transported via red blood cells and albumin, accumulating in the liver, kidneys, and intestines (10). In the liver, cadmium forms a complex with a protein known as metallothioneins. This compound then enters the bloodstream, accumulating in various organs such as the kidneys, salivary glands, prostate, cerebral cortex, testes, lungs, pancreas, breasts, and central nervous system (11, 12). It is important to note that cadmium serves no biological function in the human or animal body. In fact, it is one of the most toxic elements, known to persist in the body for an extended period of time. With a half-life ranging from 10 to 30 years, cadmium poses significant risks to human health (13). One crucial intracellular mechanism implicated in cadmium-induced carcinogenesis is oxidative stress, which leads to damage of macromolecules and ultimately contributes to various diseases, including cancer (14).

Cancers are considered as one of the most common non-communicable diseases, which annually lead to the illness and death of a large number of people worldwide (15-20). Prostate cancer is the second most common malignant cancer (after lung cancer) in men worldwide (21-26). According to the GLOBOCAN 2020 database, published in December 2020, prostate cancer accounts for 7.3% of all newly diagnosed cancer cases (27). There is evidence suggesting a potential association between occupational and environmental exposure to cadmium and the development of prostate cancer (10).

The relationship between exposure to cadmium and the occurrence of prostate cancer has been evaluated in many studies (28-38). In some studies, exposure to cadmium leads to an increased risk of prostate cancer (30, 32-35, 37-42). This is while it has been observed in other studies that exposure to cadmium reduces the risk of prostate cancer or does not have a statistically significant relationship with prostate cancer (28, 29, 31, 36, 43, 44). In condition where the results of the primary studies have heterogeneity, a systematic review study design and meta-analysis can be very helpful in obtaining a clear and transparent answer based on the available evidence.

We aimed to investigate the relationship between exposure to cadmium and the risk of prostate cancer by using a systematic review and meta-analysis.

Materials and Methods

Type of study and studied population

This systematic review and dose-response meta-analysis study was conducted using information and data from case-control, cross-sectional and cohort studies that investigated the relationship between exposure to cadmium and the risk of prostate cancer during the years 1967 to May 2022.

Search strategy and strategies

ISI web of science, Cochrane, Science Direct, Scopus, PubMed and Google Scholar were systematically searched to retrieve related articles. In these studies, contact with cadmium was consid-

ered as the exposure and the occurrence of prostate cancer as the outcome. The keywords cadmium and prostate cancer and their synonyms were used based on PubMed Mesh. During the systematic search of each electronic database, the guide and instructions specific to that database were followed.

Inclusion criteria

All the published articles with case-control, cross-sectional, and cohort design that investigated the relationship between exposure to cadmium and the risk of prostate cancer up to May 2022 in the databases of ISI web of science, Cochrane, Science Direct, Scopus, PubMed and Google Scholar were available. Only articles on human populations and published in English were considered.

Exclusion criteria

If the effect size of the relationship between exposure to cadmium and the risk of prostate cancer has not been reported in a study or cannot be calculated based on the information provided in the article, the study in question has been excluded from this review.

The method of reviewing articles and information extracted from each study

After retrieving the articles in various databases and scientific banks, all the retrieved articles were sent to endnote referencing management software, in this software, duplicated articles were identified and removed by using the possibility of repetition, and then by reading the title the remaining articles, studies that did not meet the inclusion criteria were identified and excluded. In the next step, the abstract and full text of the remaining articles for the final decision regarding the articles that are included in the analysis were examined. The information of the remaining final studies that met the criteria of our research were collected in an electronic form and recorded in the Excel environment. This information includes the name of the first author of the article, the year of publication of the study, the country where the study was conducted, the sample size of the study, the amount of cadmium exposure dose, the average age of the participants, the type of study, the source of exposure, the type of sample used for diagnosis.

Cadmium level and effect size were extracted and recorded in the form of relative risk or risk ratio or odds ratio with 95% confidence interval and the list of adapted variables in each study. In studies where the desired effect size was not reported, but there was information to calculate that index with the help of table 2*2, the effect size and the corresponding confidence interval were calculated. The effect size was reported in different studies as odds ratio (OR) or risk ratio (HR) or relative risk (RR), but because the incidence of prostate cancer is low, in this study they were all considered equivalent to each other.

Evaluation of the quality of articles

The results of more detailed studies are closer to fact, so the quality of articles should be measured by suitable method. For this purpose, to evaluate the quality of cross-sectional articles, a control case and a cohort from the New Castle-Ottawa scale checklist because We used quantitative scoring capability (45).

Checklist (NOS) New Castle-Ottawa scale is based on the approach of assigning stars according to the quality of non-interventional studies. This tool examines the study in three parts, which include selection criteria, comparability and depending on the type of study; is the outcome (in cohort studies) or exposure (in case-control studies); A series of answer options are provided for each item. For never, except the case of comparability, which allows the allocation of two stars; A maximum of one star is awarded. This scale classifies articles in terms of quality from 0 (poor articles) to 9 (excellent quality articles) (46).

Statistical Analysis

In the studies included in the meta-analysis, if there was a fundamental difference in the direction or size of the effect between different studies, heterogeneity was observed, and statistical and graphical tests were used to evaluate this issue. In the meta-analysis of chi-square (x^2) and I^2

statistical tests, respectively, to determine the presence and size of heterogeneity; was used. Therefore, to check the Statistical heterogeneity, the chi-square (x^2) and I^2 statistical tests and the accumulation chart were used to evaluate the heterogeneity graphically. A funnel plot was used for graphic representation and Egger's test and Begg's test were used to determine the presence of diffusion bias. Meta-regression method was used to determine the effect of different variables such as the year of the study, geographical location, study sample size and the quality assessment score of the articles in the difference between the results of the primary studies or in other words the heterogeneity between the results of the studies. In addition, to examine the impact of the results of each of the studies included in the meta-analysis on the result the Sensitivity analysis approach was used. All analyzes were performed by Stata statistical software (ver. 15).

Results

Articles included in the study

In the systematic search conducted in international scientific databases and information banks, in general 794 articles were retrieved. By reviewing these articles; 38 articles were excluded due to the lack of relevance of the full text of the article, 3 studies due to being a review and 4 articles due to lack of effect size reporting, and 15 articles remained (28-35, 37, 39-44). In the reference review of the articles, one related article was identified and considered in the analysis (36). Therefore, 16 articles were included in this systematic review and meta-analysis study (Fig. 1).

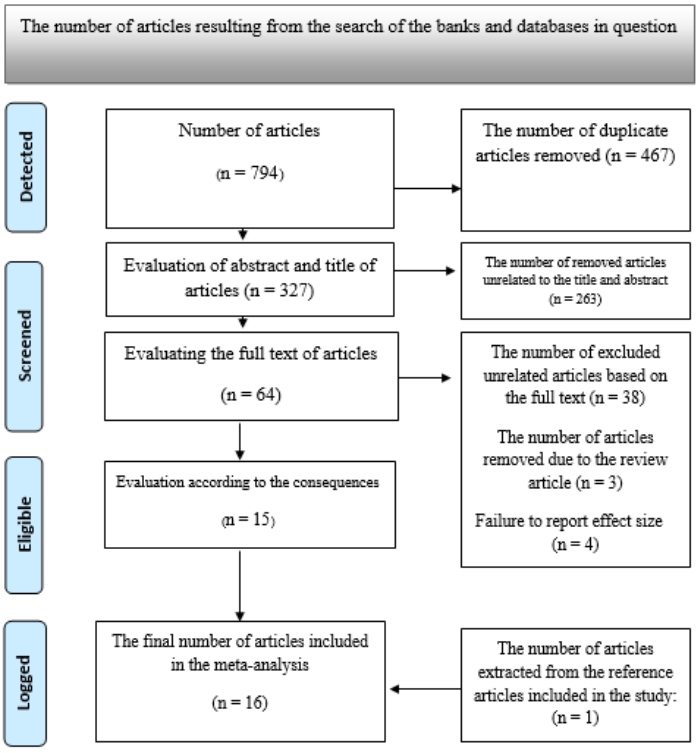

Fig. 1: Flowchart of the studies included in the meta-analysis to investigate the relationship between exposure to cadmium and the occurrence of prostate cancer

Characteristics of the included studies:

In general, 16 articles (28-37, 39-44) were included in this systematic review and meta-analysis, of which; 11 studies with case-control design (28-37, 44) and 5 studies with cohort design (39-43) were conducted. Moreover, six studies in the United States of America(28, 31, 34-36, 39), two studies in Sweden (40, 42), two studies in England (33,

37), one study in Denmark(43), one study in Japan(41), one study in Taiwan (29), one study in Italy (30), one study in Canada (44) one study in the Netherlands (32). The population studied in these studies is equal to 244,170 people (Table 1 and 2).

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

First author	*Exposure type*	*Sample*	*Exposure dose Q1*	*Exposure dose Q2*	*Odds ratio And the 95% confidence interval in the Q2*	*Exposure dose Q3*	*Odds ratio And the 95% confidence interval in the Q3*	*Exposure dose Q4*	*Odds ratio And the 95% confidence interval in the Q4*	*Quality assessment with checklist (NOS)*
Vijayakumar et al (39).	Air cadmium	Air exposure	0 (µg/l)	5.37 (µg/l)	0.85(0.63-1.14)	7.81 (µg/l)	0.97 (0.90-1.05)	13.62 (µg/l)	1.26(1.14-1.39)	8
Nyqvist et al (40).	Contamination Level in Soil	Measured in Solid	Not reported	Not reported	1.05(0.87–1.27)	Not reported	1.45(1.13–1.86)	-	-	5
Eriksen et al (43).	Dietary cadmium	Dietary Cadmium Intake	<14 (µg/day)	(14-18) (µg/day)	0.96 (0.85-1.08)	>18 (µg/day)	0.97 (0.86-1.10)	-	-	9
Sawada et al (41).	Dietary cadmium	Dietary Cadmium Intake	19.7 (µg/day)	26.7 (µg/day)	1.04 (0.80 - 1.37)	35.4 (µg /day)	1.08 (0.77 - 1.50)	-	-	9
Julin et al (42).	Dietary cadmium	Dietary Cadmium Intake	<17 (15) (µg/day)	17–20 (19) (µg/day)	1.11 (1.01-1.21)	>20 (22) (µg /day)	1.13 (1.03-1.24)	-	-	9
Jun Li et al (28).	Not reported	Urinary cadmium/creatinine	<0.534 (µg/g-cr)	>0.534 (µg/g-cr)	0.91 (0.49-1.69)	-	-	-	-	5
Chen et al (29).	Nonoccupational	Blood cadmium	≤ 0.87 (µg/l)	> 0.87 (µg/l)	1.44 (0.78-2.64)	-	-	-	-	6
Chen et al (29).	Nonoccupational	Urinary cadmium/creatinine	≤ 1.12 (µg/g-cr)	> 1.12 (µg/g-cr)	0.49 (0.31-0.78)	-	-	-	-	6
Vinceti et al (30).	Environmental and life style exposures	Toenail cadmium	<0.0073 (µg/g)	(0.0073–0.0145) (µg/g)	0.5 (0.1–2.5)	(0.0145–0.0306) (µg/g)	1.3 (0.3–4.9)	≥0.0306 (µg/g)	4.7 (1.3–17.5)	8
Platz et al (31).	Dietary cadmium	Toenail cadmium	10.8 (µg/l)	28.7 (µg/l)	0.56(0.28–1.13)	54.5 (µg/l)	0.46(0.22–0.95)	104.4 (µg/l)	0.74(0.38–1.44)	9
Aronson et al (44).	Occupational exposures	Exposed occupational Exposure	Not reported	Not reported	0.83(0.28-2.48)	-	-	-	-	9
Vandergulden et al (32).	Occupational exposures	Exposed occupational Exposure	Not reported	Not reported	2.76 (1.05-7.27)	-	-	-	-	6
Rooney et al (33).	Occupational exposures	Exposed occupational Exposure	Not reported	Not reported	1.06 (0-46 - 2.30)	-	-	-	-	6
West et al (34).	Dietary cadmium	Dietary Cadmium Intake	<36 (ug)	(36 - 48) (ug)	1.503(1.047-2.158)	(49-61) (ug)	1.014(0.701-1.465)	>61 (ug)	1.394(0.973-1.998)	7
Elghany et al (35).	Occupational exposures	Exposed occupational Exposure	Not reported	Not reported	1.3(0.6-2.7)	-	-	-	-	8
Checkoway et al (36).	Occupational exposures	Exposed occupational Exposure	Not reported	Not reported	0.79(0.01-15.78)	-	-	-	-	5
Armstrong et al (37).	Occupational exposures	Exposed occupational Exposure	Not reported	Not reported	1.55 (0.49-4.93)	Not reported	1.35 (0.31-5.91)	-	-	7

Table 2: Adjust variables to investigate the relationship between cadmium and the risk of prostate cancer

No.	*First author*	*Year*	*Adjust variables*
1	Vijayakumar et al(39).	2021	Age at diagnosis, socio-demographic indicators at the city level, prevalence of smoking at the city level, and air quality index at the city level
2	Nyqvist et al (40).	2017	-
3	Eriksen et al (43).	2015	Education (10 years), smoking status, body mass index, waist to hip ratio and physical activity
4	Sawada et al (41).	2012	Age, region, body mass index, smoking status, frequency of alcohol consumption, physical activity in leisure time, consumption of meat, soy, vegetables and fruits.
5	Julin et al (42).	2012	Age (years), family history of prostate cancer, years of education, body mass index, waist circumference, metabolic equivalent (MET) hours per day, smoking status, energy intake (kcal), alcohol consumption, selenium, lycopene and calcium
6	Jun Li et al (28).	2009	History of cadmium exposure and stages of prostate cancer
7	Chen et al (29).	2009	Age, smoking status and medical institution providing services
8	Vinceti et al (30).	2007	Body mass index, socio-economic status, smoking, family history of prostate cancer, intake of dietary nutrients, selenium, copper and zinc.
9	Platz et al (31).	2002	Residual cadmium dose
10	Aronson et al (44).	1996	Age, ethnicity, economic and social status, Quetelet index
11	Vandergulden et al (32).	1995	Age
12	Rooney et al (33).	1993	Experience working in dangerous places
13	West et al (34).	1991	-
14	Elghany et al (35).	1990	Age
15	Checkoway et al (36).	1987	-
16	Armstrong et al (37).	1985	-

Evaluation of the relationship between exposure to cadmium and the occurrence of prostate cancer

Compared to individuals exposed to cadmium in the first quartile, those exposed in the second quartile showed an odds ratio of 1.03 (95% CI: 0.95-1.12; *P*=0.493) for prostate cancer (28-37, 39-44) . Similarly, individuals exposed in the third quartile had an odds ratio of 1.12 (95% CI: 0.99-1.26; *P*=0.067) (30, 31, 34, 37, 39-43), while those exposed in the fourth quartile had an odds ratio of 1.16 (95% CI: 0.79-1.71; *P*=0.453) (30, 31, 34, 39). In other words, individuals exposed to higher doses of cadmium, specifically in the second, third, and fourth quartiles, demonstrated a 3%, 12%, and 16% increased risk of prostate cancer, respectively. However, it is important to note that these increases are not statistically significant (Fig. 2).

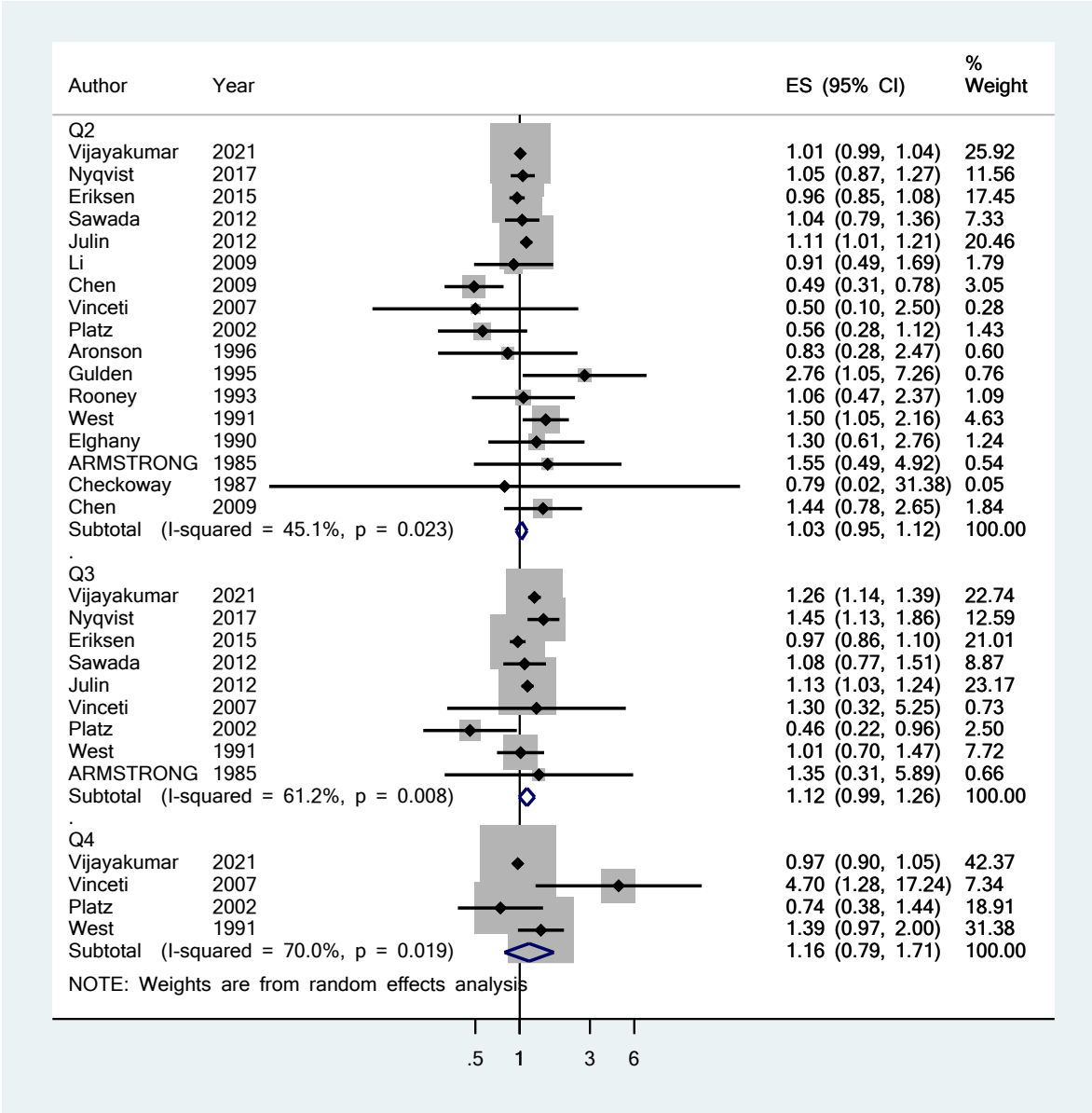

Fig. 2: Accumulation diagram of the relationship between cadmium and the risk of prostate cancer in the group exposed to the second, third and fourth quartiles of cadmium

Publication bias

In examining the relationship between prostate cancer and exposure to cadmium in the group exposed to the second quartile of exposure (Begg's test (*P*=0.787) and Egger's test (*P*=0.989)) the third quartile of exposure (Begg's test (*P*=0.835) and Egger's test (*P*=0.658)) and the fourth quartile of exposure (Begg's test (*P*=0.986) and Egger's test (*P*=0.340)) publication bias was not observed. Moreover, the funnel diagram to investigate the publication bias in the investigation of the relationship between exposure to different dose quartiles of exposure to cadmium and the chance of prostate cancer can be seen separately in Fig. 3-5.

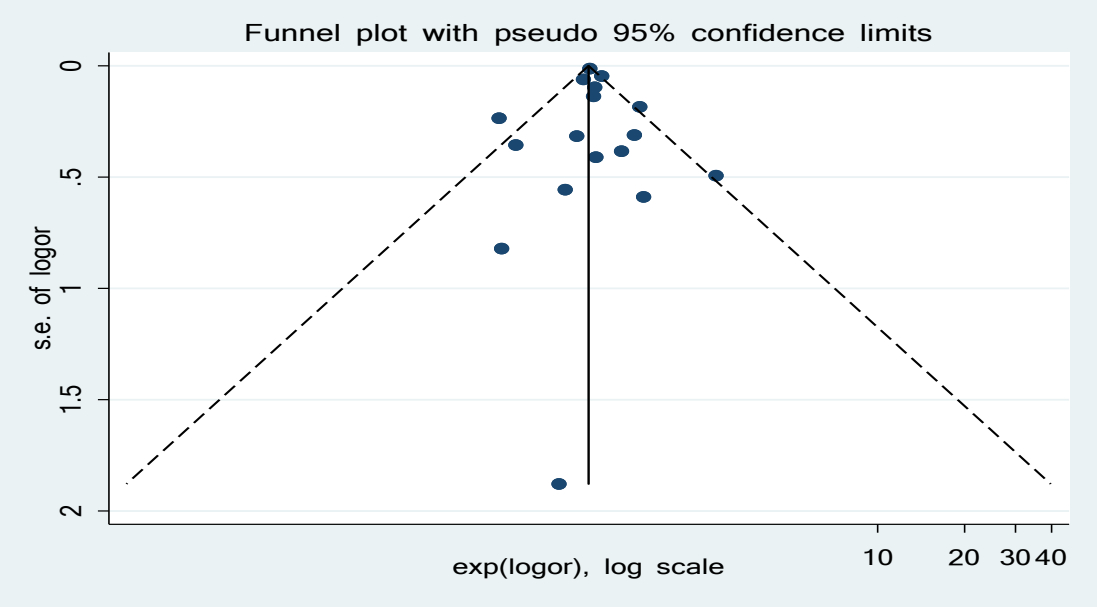

Fig. 3: Evaluating the publication bias in examining the relationship between exposure to cadmium in the second quartile of the dose exposure to prostate cancer

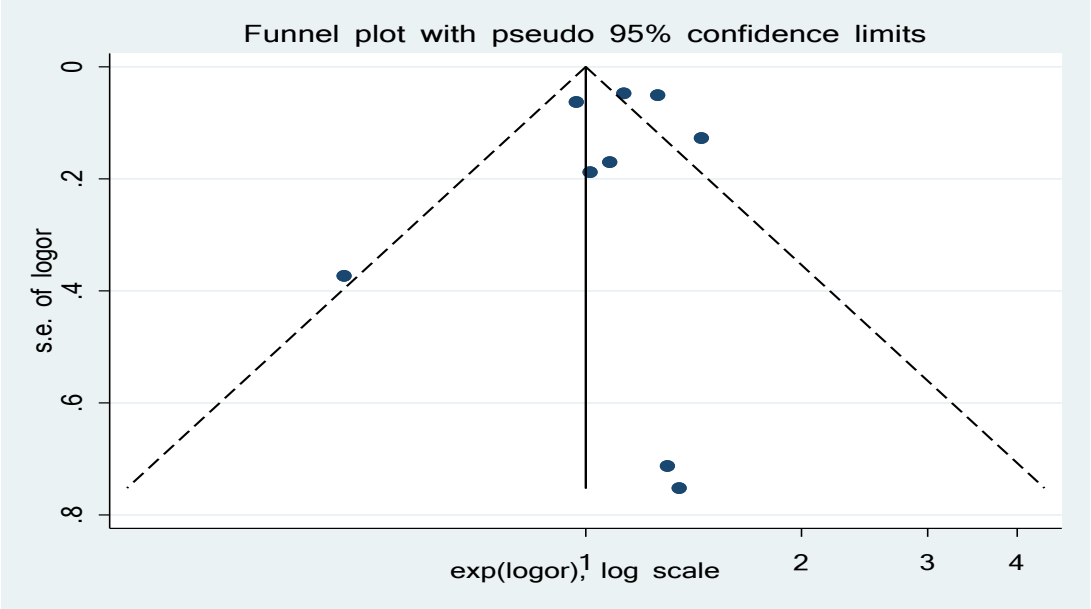

Fig. 4: Evaluating publication bias in examining the relationship between exposure to cadmium in the third quartile of the dose exposure to prostate cancer

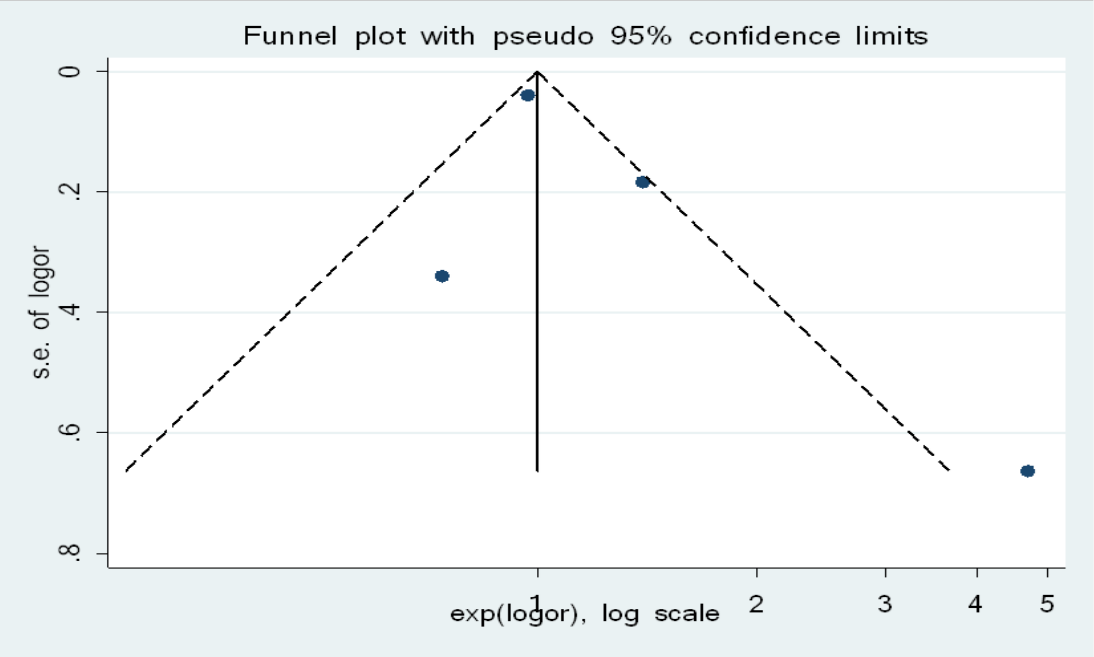

Fig. 5: Evaluating publication bias in examining the relationship between exposure to cadmium in the fourth quartile of the dose exposure to prostate cancer

Meta-regression

In order to assess the potential sources of heterogeneity among the results of various studies investigating the relationship between cadmium exposure levels and the occurrence of prostate cancer, a meta-regression analysis was conducted. This analysis incorporated variables such as the year of the study, geographical location, sample size, and quality assessment score of the articles. However, the results of the meta-regression analysis did not reveal any significant sources of heterogeneity (P=0.10) (Table 3).

Table 3: Metaregression to evaluate the sources of heterogeneity in the number of studies included in the meta-analysis

Variables	*second quarter*	*third quarter*
	***P*-value**	***P*-value**
Year	0.324	0.618
Geographical location	0.844	0.498
Study volume	0.740	0.754
Study quality assessment score	0.911	0.142

*Because the number of articles that measured the desired relationship in the fourth quartile was small, meta-regression was not performed in the fourth quartile of exposure

Sensitivity analysis

The estimated odds ratio at various levels of cadmium exposure remained unaffected by the results of any individual studies included in the analysis. This finding suggests a certain level of robustness in the results of the meta-analysis (Fig. 6 to 8).

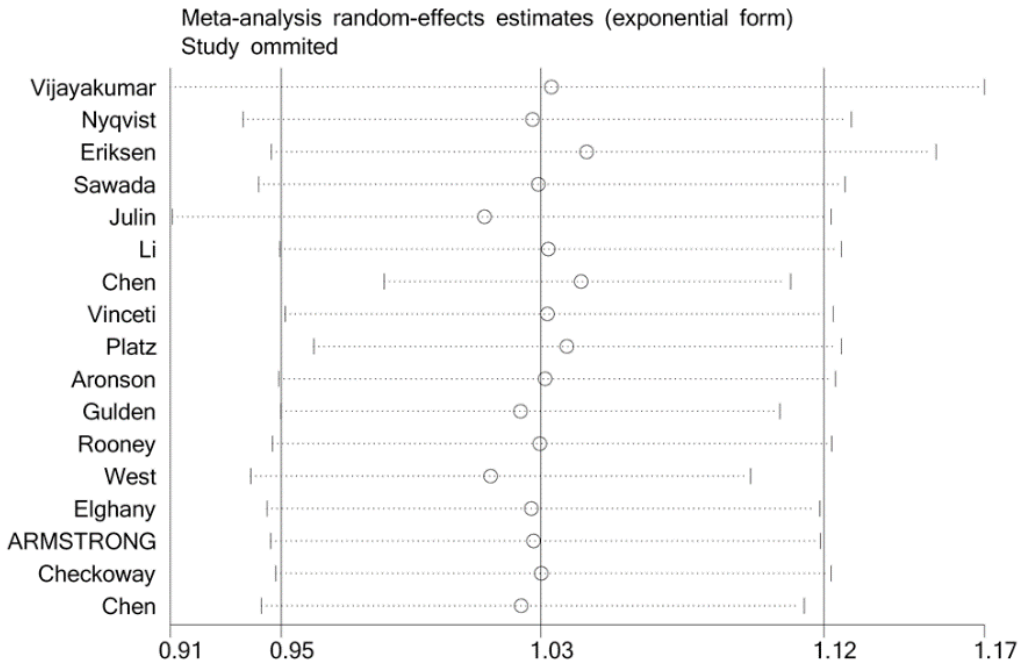

Fig. 6: Sensitivity analysis of the relationship between exposure to cadmium and the occurrence of prostate cancer- the second quartile of exposure

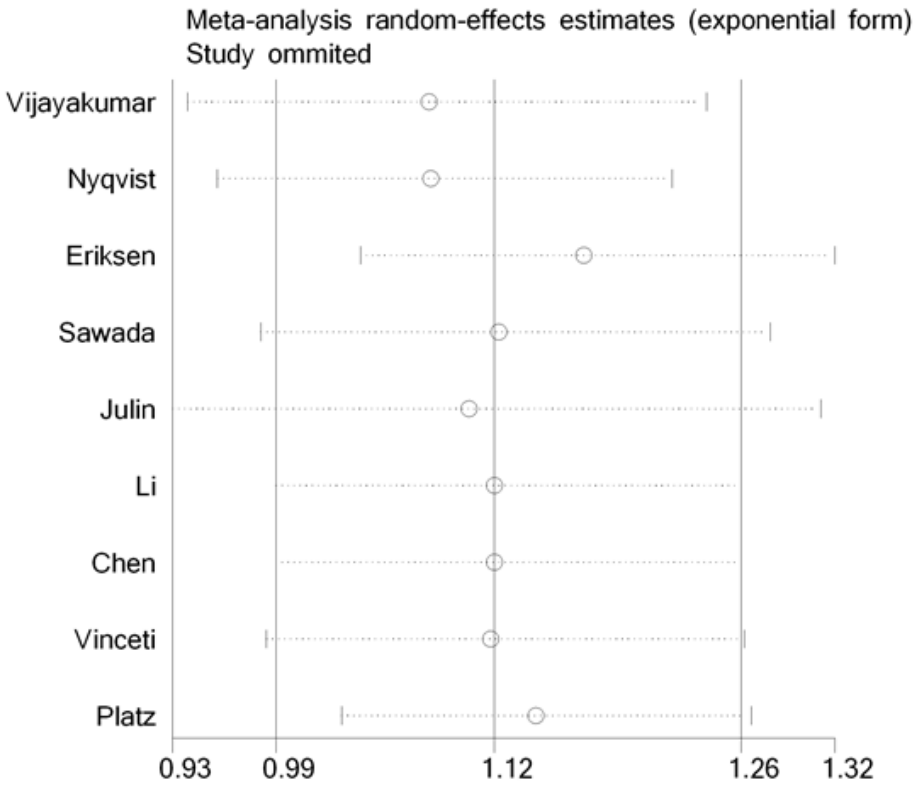

Fig. 7: Sensitivity analysis of the relationship between exposure to cadmium and the occurrence of prostate cancer - the third quartile of exposure

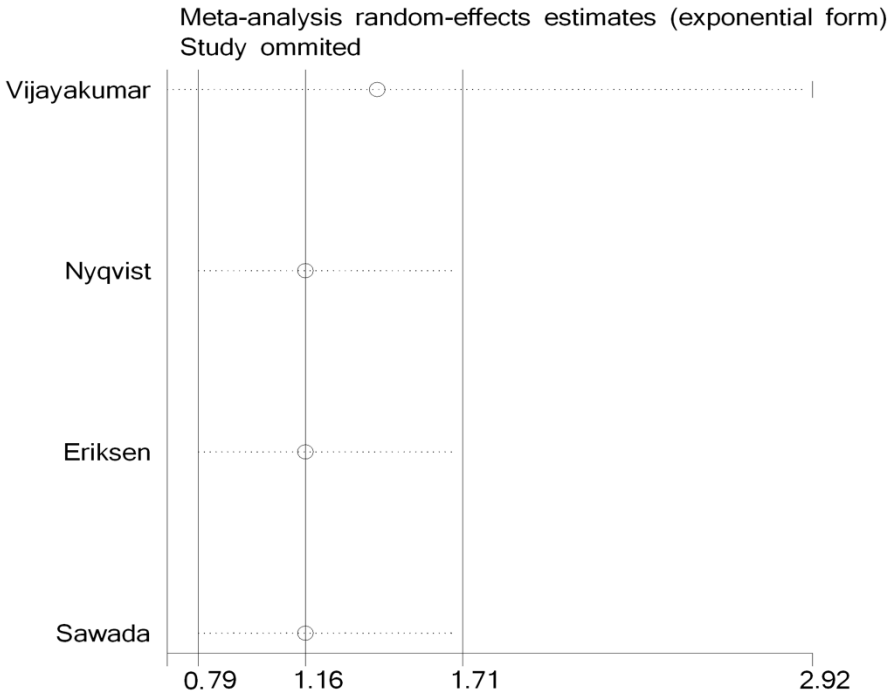

Fig. 8: Sensitivity analysis of the relationship between exposure to cadmium and the incidence of prostate cancer - the fourth quartile of exposure

Discussion

A systematic review and meta-analysis were conducted on all existing studies with inclusion and exclusion criteria (28-37, 39-44). In this study, compared to the first quarter of exposure. The odds ratio of prostate cancer in the second quartile is 1.03 (0.95-1.12), in the third quartile it is 1.12 (0.99-1.26) and in the fourth quartile it is1.16 (0.79-1.70). Although increasing the level of exposure to cadmium increases the risk of prostate cancer, this increase is not statistically significant.

Cadmium, a heavy metal, has been found to accumulate in the human body, particularly in the liver and kidneys. It has a long half-life of 10 to 30 years, meaning it can remain in the body for an extended period of time. In the body, cadmium binds to a protein called metallothionein(47), which helps regulate the levels of heavy metals like zinc (48). The carcinogenic mechanisms of cadmium involve several factors. Firstly, cadmium induces oxidative stress, leading to damage to DNA. This can result in genetic mutations and the development of cancer. Additionally, cadmium can affect cell growth and proliferation, as well as apoptosis (cell death). These disruptions in cellular processes can contribute to the development of prostate cancer (49). Furthermore, cadmium has been found to have androgenic activity, meaning it can mimic the effects of androgens (male hormones) in the body. When prostate cells come into contact with cadmium, it can stimulate cell growth, increase gene expression, and activate the androgen receptor. Over time, these effects can contribute to the development of prostate cancer (11).

Epidemiological studies do not convincingly show that cadmium exposure is a risk factor for prostate cancer (50). Occupational studies have examined the relationship between exposure to high levels of cadmium and prostate cancer risk, and many, but not all, have found that cadmium exposure is a risk factor for prostate cancer. Studies have also reported the relationship between exposure to low levels of cadmium and prostate cancer in general inconclusive(51). A cohort study, evaluated the relationship between cadmi-

um intake from food and the risk of prostate cancer, did not show a statistically significant relationship between the exposure variable and the outcome, such that the relative risk of prostate cancer per 10 micrograms of increased exposure level per day to cadmium; It was equal 0.98 (95% CI: 0.88-1.10). In addition, the mentioned relationship did not change based on the type of disease (aggressive/non-aggressive), education level, smoking status, BMI, zinc or iron consumption (43).

Based on a systematic review and meta-analysis study (52), exposure to high levels of cadmium in the general population is not associated with an increased risk of prostate cancer. The odds ratio of prostate cancer in individuals exposed to high levels of cadmium compared to those exposed to low levels was 1.22 (95% CI: 0.91-1.64), but this increased risk is not statistically significant considering the confidence interval. Additionally, receiving high levels of cadmium through nutrition does not lead to a statistically significant increase in the odds of developing prostate cancer, with an odds ratio of 1.07 (95% CI: 0.96-1.20). The study used cadmium in urine as a biomarker for long-term exposure to cadmium, and the relevant meta-analysis also showed an odds ratio of 0.86 (95% CI: 0.48-1.55) for prostate cancer in individuals with high exposure levels compared to the base group (52). Therefore, the results of this meta-analysis study align with the findings of our study.

Strengths and weaknesses of the study

In this study, it has been tried to take into account the highest sensitivity in different stages of conducting the study, and to evaluate the relationship between exposure and outcome in the form of dose-response based on exposure quartiles, however, caution should be taken in interpreting the results. Because in some studies of the reference group in the calculation of the odds ratio; The group without exposure, and in some studies, there was a group that was in the first quartile of exposure levels, in addition, in each study, the exposure level was divided into quartiles based on the range of exposure values in the same study. Therefore, in different studies, the average size of exposure in similar quartiles is not the same. Another problem in this study is that in some articles the desired effect size was not reported, in these cases, we tried to calculate the relevant effect size based on other information provided in the text of the article and include it in the final meta-analysis.

Conclusion

The increase in the level of exposure to cadmium, although briefly, leads to an increase in the risk of prostate cancer, but this increase is not statistically significant. However, to obtain more reliable results, it is necessary to conduct cohort studies with a suitable sample size in people exposed to different levels of cadmium in their daily life and work, so that a logical judgment can be made based on them with appropriate scientific support.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Data availability

The data used in this systematic review and meta-analysis can be retrieved in the tables provided in the text of the article. In addition, the data used for meta-analysis in the present study is freely available in the text of the articles used.

Conflicts of interest

There is no conflict of interest in this study.

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