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SYSTEMATIC REVIEW AND META-ANALYSIS

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Association Between Cd Exposure and Risk of Prostate Cancer

A PRISMA-Compliant Systematic Review and Meta-Analysis

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Abstract: Several observational studies on the association between Cd exposure and risk of prostate cancer have yielded inconsistent results. To address this issue, we conducted a meta-analysis to evaluate the correlation between Cd exposure and risk of prostate cancer.

Relevant studies in PubMed and Embase databases were retrieved until October 2015. We compared the highest and lowest meta-analyses to quantitatively evaluate the relationship between Cd exposure and risk of prostate cancer. Summary estimates were obtained using a random-effects model.

In the general population, high Cd exposure was not associated with increased prostate cancer (OR 1.21; 95% CI 0.91–1.64), whereas the combined standardized mortality ratio of the association between Cd exposure and risk of prostate cancer was 1.66 (95% CI 1.10–2.50) in populations exposed to occupational Cd. In addition, high D-Cd intake (OR 1.07; 95% CI 0.96–1.20) and U-Cd concentration (OR 0.86; 95% CI 0.48–1.55) among the general population was not related to the increased risk of prostate cancer. In the dose analysis, the summary relative risk was 1.07 (95% CI 0.73–1.57) for each 0.5 μg/g creatinine increase in U-Cd and 1.02 (95% CI 0.99–1.06) for each 10 μg/day increase of dietary Cd intake. However, compared with nonoccupational exposure, high occupational Cd exposure may be associated with the increased risk of prostate cancer.

This meta-analysis suggests high Cd exposure as a risk factor for prostate cancer in occupational rather than nonoccupational populations. However, these results should be carefully interpreted because of the significant heterogeneity among studies. Additional large-scale and high-quality prospective studies are needed to confirm the association between Cd exposure and risk of prostate cancer.

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Abbreviations: Cd = cadmium, CI = confidence interval, D-Cd = dietary Cd, HR = hazard risk, NOS = Newcastle–Ottawa scale, OR = odds ratio, RR = relative risk, SMR = standardized mortality ratio, U-Cd = urinary Cd.

INTRODUCTION

Prostate cancer is one of the most common malignancies in developed countries and is the second most common cancer in men, following lung cancer, worldwide.[1,2] The incidence and mortality rates of prostate cancer vary markedly among different ethnic groups, with the lowest rates found in China and other parts of Asia and the highest rates detected in Western populations.[3,4] These differences are caused by genetic susceptibility, exposure to unknown external risk factors, differences in health care and cancer registration, or a combination of these factors. In 2015, up to 220,800 men were diagnosed with prostate cancer, and 27,540 men will die of it in the United States.[2] In recent decades, a rapid increase in prostate cancer incidence has been observed in fast-developing countries, in which lifestyles have significantly changed. The etiology of prostate cancer comprises multiple factors. Some causative risk factors for prostate cancer have been implicated, including obesity, androgen, and exposure to selenium, lycopene, vitamins D and E, dietary fat, and Cd.[5–7]

Cd is a minor metal found naturally in the earth's crust and has been widely distributed in the environment as a result of anthropogenic activity. Cd presents an elimination half-life of 10 to 30 years and may exert a wide range of negative effects on human health.[8] Besides being a carcinogen,[9] Cd exposure is associated with osteoporosis and bone fracture,[10,11] type 2 diabetes,[12] kidney disease,[13] and cardiovascular disease.[14,15] Cd is currently one of the most extensive occupational and environmental pollutants. Occupational Cd exposure is used in various industries, such as Cd-emitting industries and metal mines. Occupational Cd exposure occurs when dust and fumes are inhaled. In particular, major sources of natural and anthropogenic Cd in the general population include cigarette smoking and diet choices: tobacco, grains, potatoes, and vegetables taking up Cd from the soil.[16] Several epidemiologic studies investigating the association between Cd exposure and susceptibility to prostate cancer have yielded inconsistent findings. Some studies have demonstrated a significant correlation[17–22] or little association[23–25] between Cd exposure and risk of prostate cancer, but others failed to show any significant

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association.[26–39] Therefore, we systematically performed a meta-analysis by combining all available data from observational studies to evaluate the association between Cd exposure and risk of fracture. Our meta-analysis followed the Preferred Reporting Items for Systematic Reviews.[40]

METHODS

This article presents a systematic review and meta-analysis of previously published studies; therefore, ethical approval and written informed consent from patients are not required. This research was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[40]

Data Source and Search Strategy

We searched the PubMed and Embase databases until October 2015 to identify relevant studies that evaluated the association between Cd exposure and prostate cancer risk. We used the following search terminologies: ''prostate carcinoma'' OR ''prostatic cancer'' OR ''prostate cancer'' OR ''prostatic carcinoma'' combined with ''Cadmium.'' The search was limited to human subjects. Moreover, we manually searched the reference lists of previous reviews and related article references to identify other potentially eligible studies.

Eligibility Criteria and Study Selection

The inclusion criteria were as follows: (1) Cd was the heavy metal used for exposure to humans; (2) the outcome of interest was prostate cancer incidence, prevalence, and mortality; (3) the report was a cohort, case-control study; and (4) the relative risk (RR), odds ratio (OR), hazard risk, or standardized mortality ratio (SMR) with corresponding 95% confidence interval (CI) was reported or calculated from available data. If the study was reported more than once, we included the study with the most comprehensive data.

Data Extraction and Quality Assessment

Two authors (JKS and DBY) separately extracted data from selected studies, and discrepancies were resolved through discussion and consensus. For each study, we extracted the first author's name, year of publication, study design, country, total number of cases and subjects, sex, exposure type of Cd, and adjusted variables. When more than 1 adjusted OR was reported, the OR with the most fully adjusted model was selected. For dose analysis, the number of cases and participants of person-years for each category of Cd exposure must also be provided (or data available for calculations).

We evaluated the methodological quality of the included studies by using the Newcastle–Ottawa scale (NOS).[41] The checklist contained 9 items for case-control studies and cohort studies, with every item accounting for 1 point. We considered high-quality studies as those with a score of >5.

Statistical Analysis

Differences were expressed as OR with 95% CI for non-occupational exposure studies and SMR with 95% CI for occupational exposure studies. Prostate cancer caused by Cd was considered a rare event, and the RR in the cohort study was considered as approximations of OR. Three studies reported stratified risk estimates by age[23] and region.[19,38] We combined these estimates by using a random-effects model and used the pooled estimates for the meta-analysis. The OR in 1 study[34] was not extracted; thus, we computed the crude risk estimates and their corresponding CI. A random-effects model of the DerSimonian and Laird method was used to calculate the summary risk estimates, irrespective of heterogeneity, which incorporated both within-study and between-study variability.[42] Subgroup analysis was stratified by geographic region, study design, quality of NOS scale, type of outcome, and type of exposure. We conducted sensitivity analyses by omitting 1 study in each turn to investigate whether the results were attributed to 1 large study or a study with extreme results. Furthermore, we explored the heterogeneity of the different variables mentioned above through a single-variable meta-regression analysis. We conducted a 2-stage random-effects dose-response meta-analysis by using the method proposed by Greenland and Longnecker.[43] This method required that the distribution of cases, person-years, non-cases, and risk estimates within the variance are known for at least 3 quantitative exposure categories. We assigned the median values or middle point of Cd exposure for each category to the corresponding RR. If the highest category of the studies was open-ended, we assumed the range to be the same as the adjacent interval. First, we estimated a restricted cubic spline model via generalized least-square regression with 4 knots at 5%, 35%, 65%, and 95% distribution. Second, we pooled the study-specific risk estimates by using the restricted maximum likelihood method in a random-effects meta-analysis. Nonlinear relation was estimated by testing the null hypothesis, which indicated that the coefficient of the second spline is equal to 0.

We also evaluated the potential publication bias by using funnel plot and Egger tests, with a priori $P < 0.1$ indicating a significant publication.[44] If asymmetry evidence was detected, the trim-and-fill method was employed to correct the publication bias.[45] All statistical analyses were conducted using Stata version 13.1 (Stata Corp, College Station, TX).

RESULTS

Literature Search

Figure 1 shows a flow chart of the inclusion criteria. Following the development of our search strategy, we identified 478 records from PubMed and Embase databases. After excluding the duplicates and articles that did not meet the inclusion criteria, we obtained 36 articles with full-texts read for further evaluation. Five articles were duplicate publications,[17,46–49] 4 articles presented no data useful for the meta-analysis,[50–53] 2 articles were excluded because the Cd contents in prostate tissues were measured,[54,55] 2 articles were reviews,[10,56] and 1 article reported an association

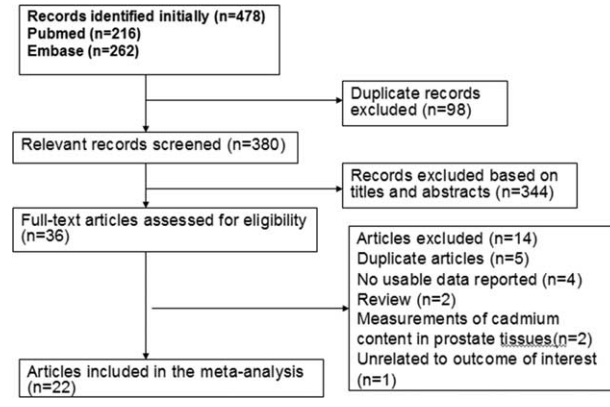

FIGURE 1. Flow diagram of the literature search and study selection.

TABLE 1. ORs/RR of prostate cancer between patients with and without environmental/occupational Cd exposure among included case-control studies

Study	Year	Country	Study design	No. of cases	No. of controls	Study period	Age, median (range), y	Exposure assessment	Effect size		Adjustment for covariates
									OR/RR	95% CI	
Armstrong	1985	United Kingdom	A case-control study	39	115	NA	NA	Occupational Cd exposure by work history information	OR 1.35	0.31–5.91	Unadjusted
Checkoway	1987	United States	A case-control study	40	40	1984–1985	68.1 (≥50)	Occupational Cd exposure by a structured questionnaire	OR 0.79	0.01–15.78	Unadjusted
West	1991	United States	A population-based case-control study	358	679	1984–1985	NA (45–74)	Dietary Cd exposure by 183 FFQ	OR 1.1 (males 45–67 years old) OR 1.8 (males 45–67 years old)	0.7–1.9	Unadjusted
Rooney	1993	United Kingdom	A case-control study	136	404	1946–1986	NA	Occupational Cd exposure by occupational health, personnel, and radiation records held by the United Kingdom Atomic Energy Authority	RR 1.06	0.46–2.30	Unadjusted
Van der Gulden	1995	Netherlands	A case-referent study	345	1346	1988–1990	Cases: 72 (SD 7.0); Referents: 69 (SD 8.1) 45–91	Occupational Cd exposure by questionnaire	OR 2.76	1.05–7.27	Adjusted for age
Seidler	1998	Germany	A case-referent study	192	210	NA	Cases: 71.1 (SD 8.6); Control: 69.7 (SD 8.5)	Occupational Cd exposure by self-administered questionnaire	OR 1.1	0.6–1.7	Adjusted for age, smoking, and region
Platz	2002	United States	A nested case-control study	115	227	1989–1996	NA (42–82)	Toenail Cd exposure by furnace atomic absorption with Zeeman background correction	OR 0.70	0.36–1.37	Adjusted for toenail weight using residual analysis
Vinceit M	2007	Italy	A case-control study	45	68	NA	NA	Toenail Cd exposure by Zeeman-effect corrected graphite-furnace atomic absorption spectrometer (Perkin Elmer Analyst 600)	OR 4.70	1.30–1.75	Unadjusted
Chen YC	2009	Taiwan	A hospital-based case-control study	261	267	NA	Cases: 72.1 (SD 6.8); Control: 71.3 (SD 7.2)	Urinary Cd exposure by a Perkin-Elmer Model 5100 PC atomic absorption spectrometer with Zeeman background correction	OR 2.04	1.28–3.23	Adjusting for age, smoking, medical institution from which the subjects were recruited, high family income, low beef intake, and low dairy product consumption remained as significant independent factors predicting an elevated risk of prostate cancer when D-Cd was included in the model

Cd = cadmium, CI = confidence interval, D-Cd = dietary cadmium, FFQ = food-frequency questionnaire, NA = not available, OR = odds ratio, RR = relative risk, SD = standard deviation.

TABLE 2. Standardized mortality ratios of prostate cancer patients with and without occupational Cd exposure among included cohort studies

Study	Year	Country	Study design	No. of cases	Cohort size	Study period	Outcome studies	Exposure assessment	Industry ype	Prostate cancer results	
										Observed/expected deaths or cases	SMR (95% CI)
Kipling	1967	Sweden	Cohort	4	248	1966	Mortality	NA	Production of cadmium pigment	4/0.58	6.90 (1.88–17.66)
Kjellstrom	1979	Sweden	Cohort	6	363	1940–1975	Mortality	Occupational Cd exposure by company records	Production of cadmium-nickel battery factory, and production of cadmium-copper alloy factory	2/1.2 (cadmium-nickel battery factory workers) 4/2.69 (cadmium-copper alloy factory workers)	1.67 (0.20–6.02) 1.49 (0.41–3.81)
Sorahan	1982	United Kingdom	Cohort	8	3025	1946–1981	Mortality	Occupational Cd exposure by company records	Production of nickel-cadmium battery	8/6.6	1.21 (0.52–2.34)
Thun	1983	United States	A retrospective cohort	3	292	1940–1969	Mortality	Occupational Cd exposure by company records	Production of cadmium metal and compounds in the smelter	3/1.41	2.13 (0.44–6.22)
Elinder	1985	Sweden	Cohort	28	522	1951–1983	Mortality	Occupational Cd exposure by questionnaire	Production of nickel-cadmium battery in the plant	28/17.2	1.62 (1.08–2.35)
Kazatzis	1988	United Kingdom	Cohort	30	6995	1943–1984	Mortality	Occupational Cd exposure by company records	Production of nickel-cadmium battery and copper-cadmium alloy	30/33.2	0.90 (0.61–1.29)
Jarup	1998	Sweden	Cohort	11	869	1940–1992	Mortality	Occupational Cd exposure by company records	Production of nickel-cadmium battery in the plant	11/9.0	1.22 (0.35–3.30)
Elliott	2000	United Kingdom	Cohort	33	611	1939–1997	Mortality	Occupational Cd exposure by resident records	Exposure to high concentrations of cadmium in the soil	12/NA (Shipham) 21/NA (Hutton)	2.57 (1.46–4.52) 1.32 (0.86–2.02)

Cd = cadmium, CI = confidence interval, NA = not available, SMR = standardized mortality ratios.

TABLE 3. OR/RR/HR of prostate cancer between patients with and without environmental/occupational Cd exposure among included cohort studies

Study	Year	Country	Study design	No. of cases	Cohort size	Study period	Outcome studies	Exposure assessment	Age, Median (range), y	Effect size		Adjustment for covariates
										OR/RR/SMR	95% CI	
Julin B	2012	Sweden	A population-based cohort study	3085	41,089	1998–2009	Incidence	D-Cd exposure by 96 items FFQ	56.2 (45–79)	RR 1.13	1.03–1.24	Adjusted for attained age, family history of prostate cancer (yes, no), years of education (≥12, <12 years), BMI (18.5–<25, 25–<30 and ≥30 kg m^{-2}), waist circumference (<94, 94–<102 and ≥102 cm) (WHO, 2000), metabolic equivalent hours (MET) hours per day (quartiles), smoking status (ever, never), total energy intake (kcal cont.) and alcohol consumption (<0.1, 0.1–<5, 5–<10, 10–<15 and ≥15 g per day).
Sawada N	2012	Japan	A population-based prospective cohort study	470	46,033	1990–1998	Incidence	D-Cd exposure by 138 items FFQ	NA (45–74)	HR 1.08	0.77–1.50	Adjusted for age; area; body mass index; smoking status; frequency of alcohol intake; leisure-time; physical activity; intake of meat, soybean, vegetable, and fruit; menopausal status; and use of exogenous female hormones.
Lins YS	2013	United States	Cohort study (NHANES)	61	2474	1988–1984	Mortality	U-Cd exposure by graphite furnace atomic absorption spectrometry (Perkin-Elmer Corp., Norwalk, CT)	NA (≥50)	HR 2.39	0.83–6.86	Adjusted for sampling weight
Garcia Esquinas	2014	United States	A prospective cohort study (Strong Heart Study)	16	3792	1989–1991	Mortality	U-Cd exposure by coupled plasma mass spectrometry (Agilent 7700x ICP-MS; Agilent Technologies, Waldbronn, Germany)	NA (45–75)	HR 0.48	0.11–2.08	Adjusted for sex, age, smoking status (never, former, current), cigarette pack-years (continuous), and BMI (<25, 25–30, ≥30 kg/m^2).
Eriksen KT	2015	Sweden	A prospective cohort study (DCH)	1567	26,778	1993–2010	Incidence	D-Cd exposure by 192 items FFQ	NA (50–65)	RR 0.97	0.86–1.10	Adjusted for educational level (<8 y; 8–10y; >10y), smoking status (never; former; current), BMI (continuous), waist-to-hip ratio (continuous), and physical activity (MET score, continuous)

BMI = body mass index, Cd = cadmium, CI = confidence interval, D-Cd = dietary cadmium, DCH = , FFQ = food-frequency questionnaire, HR = hazard ratio, MET = metabolic equivalent, NA = not available, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, RR = relative risk, SD = standard deviation, U-Cd = urinary Cadmium.

between Cd and prostate-specific antigen.[57] Finally, 22 studies that met the meta-analysis criteria were included.

Study Characteristics

Tables 1–3 present the characteristics of the included studies. A total of 22 studies, comprising 8 case-control and 14 cohort studies, contributed to the meta-analysis. These studies were published from 1967 to 2015. The number of prostate cancer patients ranged from 40 to 358 in the case-control studies and from 3 to 83,085 in the cohort studies. Thirteen studies were conducted in Europe,[18–22,29,30,32,35–39] 7 in the United States,[23,24,26,27,31,33,34] and 2 in Asia.[25,28] Thirteen studies reported findings for prostate cancer incidence,[18,20,22–25,28,33–37,39] whereas the remaining 9 studies reported results for prostate cancer mortality.[19,21,26,27,29–32,38] We included a total of 200 prostate cancer deaths, 6653 prostate cancer cases, and 137,998 participants in the meta-analysis. Eight studies were designed to evaluate OR,[20,23–25,33–36] 3 evaluated RR,[18,37,39] 3 evaluated hazard risk,[26–28] and 8 evaluated SMR[19,21,22,29–32,38]. Three articles used urinary Cd (U-Cd) as biomarker for long-term exposure to Cd,[25–27] 4 articles evaluated Cd levels by estimating the dietary Cd (D-Cd) by using food frequency questionnaires,[18,23,28,39] and 2 studies examined Cd in toenails[20,33]. Twelve studies reported an association between occupational Cd exposure and prostate cancer risk,[19,21,22,24,29–32,34–38] whereas 10 studies used nonoccupational populations.[18,20,23,25–28,33,36,39] Most of the studies were controlled for some conventional risk factors, including age (n = 6) and smoking (n = 6). Some studies were also controlled for body mass index (n = 3) and alcohol consumption (n = 2), but few studies were adjusted for beef intake, dairy product consumption (n = 1), and intake of vegetable and fruit (n = 1). None of the studies were adjusted for other heavy metals, trace elements of organic pollutants, and intake of grains.

NOS was used to assess the quality of studies included in the meta-analysis (Table 4). The median NOS score was 4.8 (range 3–7).

Results From Pooled SMR Estimates With and Without Population Exposed to Occupational Cd

Figure 2 shows the SMR estimates and 95% CI from each study, as well as the pooled SMR estimate based on a random-effects model. Results from the 8 cohort studies indicated that the pooled SMR was 1.66 (95% CI 1.10–2.50) with moderate heterogeneity ($P_{\text{for·heterogeneity}} = 0.002$; $I^2 = 69.9\%$). In subgroup analyses for exposure type, we restricted each analysis to 7 occupational exposure studies, resulting in a summary SMR of prostate cancer of 1.61 (95% CI 1.04–2.48). Only 1 study was conducted in the United States,[31] and the 7 other studies were conducted in Europe. When we stratified the analysis by geographic region, the pooled SMR was 1.63 (95% CI 1.05–2.52) for studies conducted in Europe. Compared with a low NOS score (SMR = 2.08, 95% CI 0.73–5.91), the association was higher among studies with high NOS score (OR = 1.51, 95% CI 1.14–1.98) (Table 5). In a sensitivity analysis, similar results were observed, which ranged from 1.30 (95% CI 1.03–1.64) with low heterogeneity ($I^2 = 9.0\%$, heterogeneity $P = 0.360$) (excluding the study by Kipling et al[22]) to 1.87 (95% CI 1.23–2.83) with significant heterogeneity ($I^2 = 58.4\%$, heterogeneity $P = 0.025$) (excluding the study by Kazantzis et al[30]). Egger test ($P = 0.241$) and funnel plot (Figure 3) showed no publication bias.

TABLE 4. Quality assessment of eligible studies based on Newcastle–Ottawa scale

Author	Year	Selection	Comparability	Exposure
Kipling	1967	2	0	1
Kjellstrom	1979	2	0	1
Sorahan	1982	3	0	2
Thun	1983	2	0	2
Armstrong	1985	2	0	1
Elinder	1985	3	0	2
Checkoway	1987	2	0	1
Kazantzis	1988	2	0	2
West	1991	3	0	2
Rooney	1993	3	0	1
Van der Gulden	1995	2	1	1
Jarup	1998	3	0	2
Seidler	1998	2	1	1
Elliott	2000	3	0	2
Platz	2002	2	1	2
Vinceit M	2007	3	0	2
Chen YC	2009	2	2	2
Julin B	2012	2	2	2
Sawada N	2012	2	2	2
Lins YS	2013	3	1	2
Garcia Esquinas	2014	2	2	2
Eriksen KT	2015	3	2	2

Results From Pooled OR Estimates With and Without Environmental/Occupational Cd-Exposed Population

Figure 4 shows the OR estimates, 95% CI from individual studies, and pooled OR estimate based on a random-effects model. Results from the 14 studies, comprising 9 case-control studies and 6 cohort studies, indicated that the pooled OR was 1.23 (95% CI 0.81–1.88) with significant heterogeneity ($P_{\text{for·heterogeneity}} = 0.000$; $I^2 = 96.2\%$). In subgroup analyses for study design, we restricted each analysis to 9 case-control studies and 5 cohort studies; the summary ORs of prostate

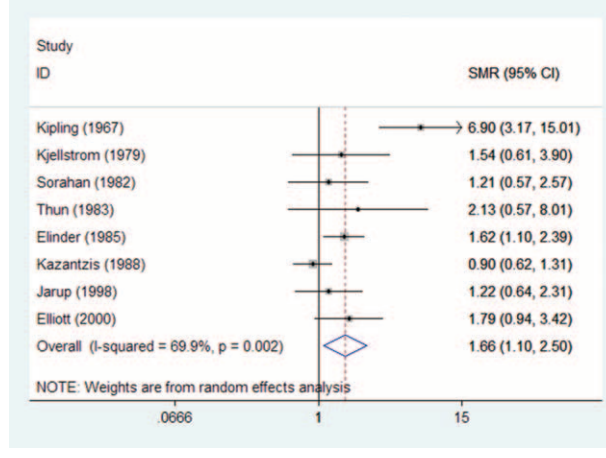

FIGURE 2. Forest plot of Cd exposure and prostate cancer risk (SMR) in occupational Cd exposure population. Cd = cadmium, SMR = standardized mortality ratio.

TABLE 5. Results of overall subgroup analysis among occupational Cd exposure populations

	Studies, N	SMR (95% CI)	*P*	*P* of heterogeneity	I^2, %
Total	8	1.66 (1.10–2.50)	0.016	0.002	69.9
Geographic location					
European	7	1.63 (1.05–2.52)	0.028	0.001	73.8
United States	1	2.13 (0.57–8.01)	0.263	NA	NA
Exposure type					
Occupational exposure	7	1.65 (1.03–2.64)	0.038	0.001	73.7
Environmental exposure	1	1.79 (0.94–3.42)	0.079	NA	NA
NOS score					
High	4	1.51 (1.14–1.98)	0.004	0.765	0.0
Low	4	2.08 (0.73–5.91)	0.171	0.000	86.3

CI = confidence interval, NA = not available, NOS = Newcastle–Ottawa scale, SMR = standardized mortality ratios.

cancer for the highest category of Cd exposure versus the lowest category were 1.31 (95% CI 0.60–2.87) and 1.06 (95% CI 0.99–1.09), respectively. Five studies were conducted in the United States, 6 in Europe, and 2 in Asia. When we stratified the analysis by geographic region, the combined OR was 1.10 (95% CI 0.66–1.84) in studies conducted in the United States, 1.57 (95% CI 0.86–2.84) in studies conducted in Europe, and 0.74 (95% CI 0.34–1.60) in studies conducted in Asia. When stratified by type of Cd exposure, the combined OR of prostate cancer was 1.05 (95% CI 0.97–1.15) for D-Cd, 1.18 (95% CI 0.28–2.34) for U-Cd, and 1.87 (95% CI 0.29–12.06) for toenail Cd. Five studies reported an association between occupational Cd exposure and prostate cancer risk; however, the association was not significant in the occupational exposure population (OR = 1.31, 95% CI 0.79–2.19). When stratified by type of outcome, the combined OR was 1.23 (95% CI 0.78–1.95) for prostate cancer incidence and 1.29 (95% CI 0.51–3.27) for prostate cancer mortality. Compared with studies that presented low NOS scores (OR = 1.27, 95% CI 0.87–1.875), the association was higher among studies with high NOS scores (OR = 1.18, 95% CI 0.71–1.96) (Table 6). Six studies[18,25,26,28,35,39] were adjusted for smoking status, resulting in pooled OR of 0.96 (95% CI 0.80–1.16) with moderate heterogeneity ($P_{\text{for heterogeneity}} = 0.007$; $I^2 = 68.8\%$). Sensitivity analysis showed that the overall pooled estimate was not altered substantially, with the exclusion of 1 study. The overall combined OR after sequential exclusion of 1 study at a time ranged from 1.03 (95% CI 0.88–1.21) with significant heterogeneity ($P_{\text{for heterogeneity}} = 0.017$; $I^2 = 51.3\%$) (excluding the study by Vinceit et al[20]) to 1.29 (95% CI, 0.84–1.98) with significant heterogeneity ($P_{\text{for heterogeneity}} = 0.000$; $I^2 = 96.5\%$) (excluding the study by Garcia Esquinas et al [26]). No evidence of publication bias resulted from Egger test ($P = 0.881$) and near-symmetric funnel plot (Figure 5).

Considering the relatively high heterogeneity observed in the trials, a meta-regression was performed to explore the predefined possible sources of heterogeneity. None of the regression coefficients were statistically significant (Table 7), suggesting that publication year, study design, geographic region, NOS, type of outcome, and type of Cd exposure were insignificant sources of heterogeneity.

Two studies were included in the dose-response analysis of U-Cd exposure and prostate cancer risk, and a nonlinear association was not observed between them ($P_{\text{for nonlinearitytest}} = 0.47$). The summary RR per 0.5 μg/g creatinine increment was 1.07

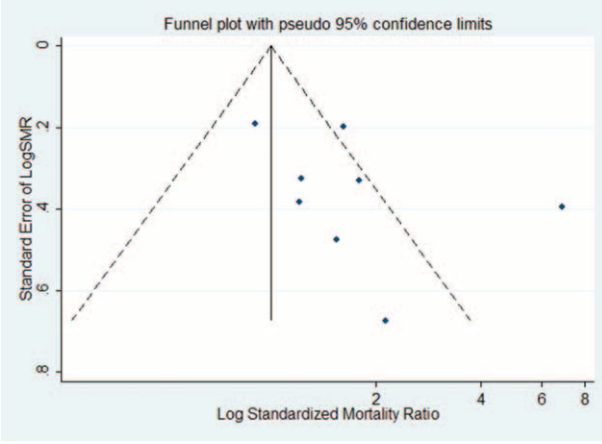

FIGURE 3. Funnel plot of Cd exposure and prostate cancer risk (SMR) in occupational Cd exposure population. Cd = cadmium, SMR = standardized mortality ratio.

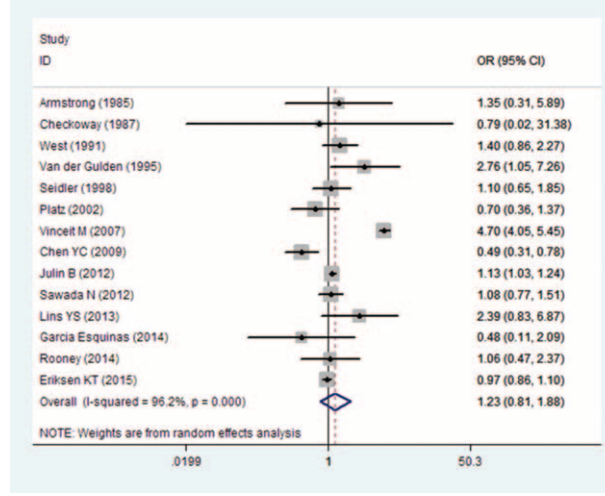

FIGURE 4. Forest plot of Cd exposure and prostate cancer risk (OR) in occupational/environmental Cd exposure population. Cd = cadmium, OR = odds ratio.

TABLE 6. Results of overall subgroup analysis among environmental/occupational Cd exposure populations

	Studies, N	OR (95% CI)	*P*	*P* of heterogeneity	I^2, %
Total	14	1.23 (0.81–1.88)	0.332	0.000	96.2
Geographic location					
European	7	1.57 (0.86–2.84)	0.141	0.000	98.1
United States	5	1.10 (0.66–1.84)	0.708	0.200	33.2
Asian	2	0.74 (0.34–1.60)	0.445	0.007	86.5
Type of exposure					
Occupational exposure Cd	5	1.27 (0.87–1.87)	0.217	0.553	0.0
Environmental exposure Cd					
Total Cd	9	1.18 (0.71–1.96)	0.522	0.000	97.6
D-Cd	4	1.07 (0.96–1.20)	0.222	0.177	39.1
U-Cd	3	0.81 (0.28–2.34)	0.698	0.025	72.9
Toenail Cd	2	1.87 (0.29–12.06)	0.221	0.000	96.6
High	9	1.18 (0.71–1.96)	0.522	0.000	97.6
Low	5	1.27 (0.87–1.87)	0.217	0.553	0.0
Type of outcome					
Incidence	11	1.23 (0.78–1.95)	0.379	0.000	97.1
Mortality	3	1.29 (0.51–3.27)	0.595	0.221	33.8
Study design					
Case-control study	9	1.31 (0.60–2.87)	0.503	0.000	94.5
Cohort study	5	1.06 (0.93–1.22)	0.374	0.129	44.0

CI = confidence interval, D-Cd = dietary cadmium, OR = odds ratio, U-Cd = urinary cadmium.

(95% CI 0.73–1.57) with no evidence of heterogeneity ($P_{\text{for heterogeneity}} = 0.33$; $I^2 = 0.0\%$). Four studies were included in the dose-response analysis of D-Cd intake and prostate cancer risk. We found no significant departure from a simple linear-response association between Cd exposure and prostate cancer ($P_{\text{for nonlinearity test}} = 0.64$). The estimated RR of prostate cancer risk was 1.02 (95% CI 0.99–1.06) for 10 μg/d increase of D-Cd, with little evidence of heterogeneity ($P_{\text{for heterogeneity}} = 0.15$; $I^2 = 40.7\%$) (Figure 6).

DISCUSSION

Cd is a nonessential metal widely distributed in the environment by industrial and agricultural activities.[8] According to accumulated evidence from experimental and epidemiologic studies, Cd has been recognized as a human carcinogen.[58,59] Recently, increasing evidence established a link between Cd exposure and prostate cancer,[33,39] breast cancer,[60–62] pancreatic cancer,[63,64] and lung cancer.[65,66] Substantial compelling evidence supported that occupational exposure to Cd resulted in lung cancer and showed similar findings regarding prostate and other cancers. A positive association between Cd exposure and prostate cancer mortality was found in 2 cohort studies[21,22] and 1 case-control study,[36] whereas several studies showed no significant association among occupational populations.[19,24,29–32,34–38] These studies were conducted in a Cd-polluted area (eg, nickel batteries, pigments, and soldering alloys). Most nonoccupational Cd exposure studies,[23,26–28,33,39] though not all,[17,18,20] showed no significant relation between Cd exposure and prostate cancer risk. Verougstraete et al[67] conducted a systematic review on Cd-exposed workers and found that Cd exposure was not associated with increased risk of prostate cancer. In another recent meta-analysis based on 8 previous studies, in which D-Cd intake showed no statistically significant association with cancer risk except in stratified analysis by geographic region, a positive association between D-Cd intake and cancer risk was observed.[56] However, few studies were included in the meta-analysis, which limited the possibility of drawing robust conclusions, especially in the subgroup analysis. Compared with the 2 previous meta-analyses, the current research presented a more extensive systematic review, which included a large number of studies with more than 6828 cases, 123 deaths, and almost 171,972 participants. Thus, we obtained adequate statistical data to clarify the relation between Cd exposure and risk of prostate cancer. In our meta-analysis, we found a positive association between high Cd exposure and risk of prostate cancer for occupational exposure, but not for nonoccupational exposure. These findings can potentially result in higher Cd exposure levels prevailing in these studies.

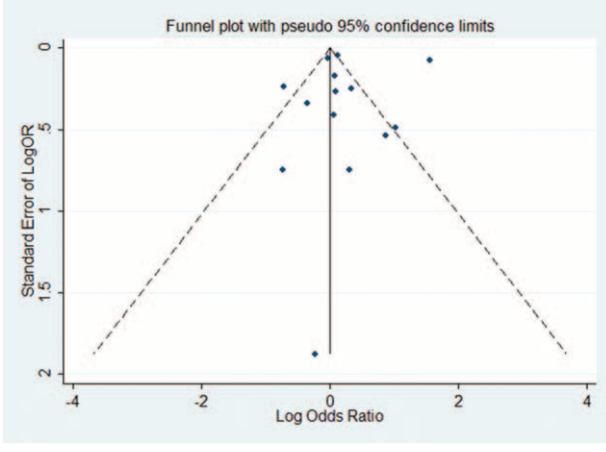

FIGURE 5. Funnel plot of Cd exposure and prostate cancer risk (OR) in occupational/environmental Cd exposure population. Cd = cadmium, OR = odds ratio.

TABLE 7. Effects of study variables on meta-regression

Covariant	Coefficient	*P*	95% CI
Geographic region (Ref = United States)			
Europe	0.375	0.407	−0.583 to 1.332
Asia	−0.379	0.513	−1.611 to 0.854
Type of Cd exposure (Ref = U-Cd)			
D-Cd	0.345	0.582	−1.108 to 1.798
Toenail-Cd	0.928	0.232	−0.780 to 2.636
Year of publication	−0.013	0.563	−0.060 to 0.034
Study design	−0.194	0.633	−1.058 to 0.670
Type of outcome	−0.025	0.965	−1.200 to 1.250
NOS quality	−0.143	0.952	−1.103 to 0.818

D-Cd = dietary cadmium, NOS = Newcastle–Ottawa scale, U-Cd = urinary cadmium.

No substantial changes were observed in most subgroup analyses because the Cd concentrations in the blood and urine are the most common biomarkers for Cd exposure. U-Cd mainly reflects Cd accumulation in the kidney, as determined by life-long exposure, whereas D-Cd demonstrates a combination of both current and historical exposure. Results from subgroup analyses stratified by type of Cd exposure showed that both U-Cd and D-Cd were not associated with increased prostate cancer risk. Smoking is a primary source of exposure in the general population and is known to damage health through direct and indirect effects. Thus, we also performed subgroup analyses among studies controlled for smoking status to minimize possible non–Cd-mediated negative effects of tobacco smoking on prostate cancer risk. Six publications were adjusted for smoking status, and the results showed that Cd exposure was not associated with increased prostate cancer risk (OR 0.94, 95% CI 0.77–1.14).

Many studies have demonstrated that the prostate is a target organ for the deposition of Cd,[68,69] and numerous experimental studies in vivo and in vitro have indicated that Cd can act as a prostate carcinogen in rats.[70] Cd has been recognized as a human carcinogen by the International Agency for Research on Cancer on the basis of mechanistic and epidemiologic evidence from high-exposure occupational settings.[9] Several mechanisms are responsible for the carcinogenesis of Cd exposure, including induction of oxidative stress,[71] suppression of DNA repair,[72] alterations of DNA methylation,[73] inhibition of apoptosis proto-oncogene activation,[74] tumor suppressor gene inactivation, and cell adhesion disruption.[75] In addition, Cd can exert estrogenic activities that play a role in the development of prostate cancer. Cd is suggested to exert estrogenic properties, and direct receptor-mediated effects of estrogen on prostate are plausible.[76] Experimental evidence showed that excessive exposure to estrogens can cause prostate cancer. In human prostate epithelial cells, Cd exhibits estrogenic activity, including proliferation of prostate cells and activation of the estrogen receptor-α.[77] Substantial evidence showed a positive relation between Cd exposure and risk of endometrial[78] and breast cancers.[79] Therefore, high Cd exposure can potentially increase the risk of prostate cancer.

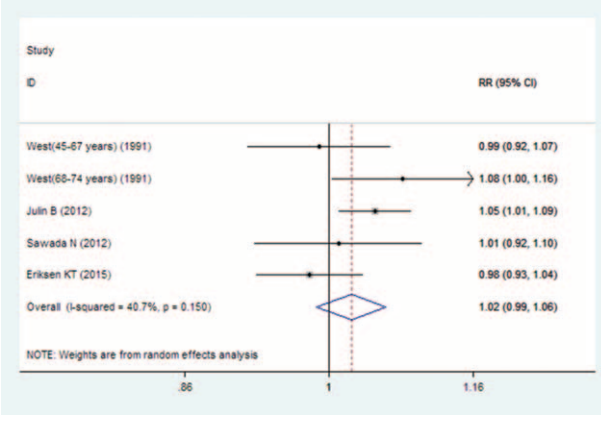

FIGURE 6. Forest plot of linear trend between dietary Cd intake and risk of prostate cancer (RR), with dose scale of 10 μg/d increase in environmental Cd exposure population. Cd = cadmium, RR = relative risk.

The present meta-analysis exhibited several strengths. The first research highlight of this meta-analysis is its large sample size. The large number of total cases provided high statistical power to quantitatively evaluate the association between Cd exposure and prostate cancer risk. Second, publication bias is a potential concern in any meta-analysis because small studies with null results do not get published. However, in our meta-analysis, we found little evidence of publication bias.

Nevertheless, some limitations should be considered in the present meta-analysis. First, observational studies, even if prospective, cannot prove causality. We cannot exclude the possibility that the observed positive relationship between Cd exposure and prostate cancer risk is attributed to confounding factors. Majority of the studies were adjusted for potential confounding factors, but not all potential confounders were adjusted in every study. For instance, a potential confounder such as cigarette smoking is not only a source of Cd but also contains other substances with adverse health effects. In analyses stratified by adjusting the smoking status, similar results were obtained. Most studies were adjusted for some conventional risk factors, including age and smoking status, and some studies were controlled for body mass index and alcohol consumption. However, few studies were adjusted for other dietary variables or nutrients, whereas none of the included studies were controlled for other heavy metals, trace elements, or organic pollutants. Second, an accurate assessment of Cd exposure remains a challenge. Most studies used questionnaires to assess Cd exposure, whereas some research used interviews, company records, and self-reports to evaluate Cd concentration. However, increasing errors in measurements become inevitable. The imprecise measurement of Cd concentration might have attenuated the true associations. Third, the definition of Cd exposure varied across studies. The Cd exposure types differed according to geographical locations, as urine Cd concentration (in μg/g creatinine) ranged from approximately 0.39 to 1.46 in the US and European population. In Asian studies, the mean urine Cd concentration (in μg/g creatinine) ranged from 0.94 to 1.4. The Cd intake from food generally varies between 9 and 25 μg/d in the US and in Europe. In Asian studies, the mean D-Cd intake (in μg/day) ranged from 19.7 to 35.4. These factors can affect our results. However, our subgroup analyses showed that the associations between Cd exposure and prostate cancer risk did not differ significantly in terms of study location. Third, potential sources of between-study heterogeneity, which is common in meta-analyses, should be explored. In sensitivity analyses, the observed heterogeneity was explained by an article[22] that reported a significant positive association and

yielded a low NOS. Results from subgroup analyses indicated that geographic region, study design, quality of NOS, type of outcome, and type of exposure are potential sources of heterogeneity. Nevertheless, we used meta-regression and sensitivity analysis to explore the potential causes of between-study heterogeneity. Our meta-regression analysis did not find covariates of publication year, study design, geographic region, NOS, type of outcome, and type of Cd exposure as sources of heterogeneity. Finally, although we selected the highest multivariable-adjusted effect estimates in our meta-analysis, we cannot exclude the possibility that the observed increase in association between Cd exposure and prostate cancer risk among occupational populations can be ascribed to unmeasured or residual confounding factors. The unstable results were observed in occupational and environmental populations, indicating that more relevant articles are needed to further explore this association.

In summary, this meta-analysis suggests high Cd exposure as a potential risk factor for prostate cancer in occupational populations but not in nonoccupational populations. However, these results should be carefully interpreted because of the significant heterogeneity among studies. Additional large-scale and high-quality prospective studies are needed to confirm the association between Cd exposure and risk of prostate cancer.

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