Association between cadmium exposure and renal cancer risk: a meta-analysis of observational studies

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Cadmium (Cd) is a widespread environmental pollutant and has been a recognized carcinogen for several decades. Many observational studies reported Cd exposure might be one cause of renal cancer. However, these findings are inconsistent. We conducted a meta-analysis to evaluate the relationship between cadmium exposure and renal cancer risk. A comprehensive PubMed and Embase search was conducted to retrieve observational studies meeting our meta-analysis criteria. A combined odds ratio (OR) and corresponding 95% confidence interval (CI) were applied to assess the association between Cd exposure and renal cancer risk. The meta-analysis showed that a high Cd exposure significantly increased renal cancer 1.47 times (OR = 1.47; 95% CI = 1.27 to 1.71, for highest versus lowest category of cadmium categories). The significant association remained consistent when stratified by geographic region and gender, however mixed results were produced when stratified by sample size, study design, NOS score, adjustment for covariates, effects measure, and exposure type. Our results indicated that a high Cd exposure was associated with increased renal cancer risk and the association was higher for occupational exposure compared with non-occupational exposure. This meta-analysis suggests that a high Cd exposure may be a risk factor for renal cancer in occupational population.

In 2015, a total of 61,560 new cases of renal cancer were diagnosed with 14,080 deaths in the USA alone, making renal cancer the sixth leading cause of cancer deaths1. The prevalence of renal cancer has been increasing by approximately 2–4% per year for the last two decades worldwide1. The advancement in imaging diagnoses and early screening do not fully explain this trend1. Among the African-American population, the incidence of renal cancers has shown a more rapid increase. Furthermore, studies estimate renal cancer will be a major concern in the male population due to a recent rise in documented cases. During the past two decades, established renal cancer risk factors, including tobacco smoking, heavy alcohol drinking, hypertension, obesity, and use of phenacetin-containing drugs were well documented as predominant etiologic factors for renal cancer3. Cadmium (Cd) is a toxic heavy metal harmful to human health found naturally at low levels in rocks and soil. Cd is accumulated in the kidney cortex and is one cause of end-stage renal disease4,5. Recently, numerous observational studies were conducted to evaluate Cd exposure effects on renal cancer susceptibility, which showed positive5–10 and null associations11–13. However, these studies had small sample sizes, which might prevent any capacity to detect an effect. Therefore, given the increased diagnosis of Cd exposure and poor prognosis of renal cancer, risk factors for renal cancer development would have a substantial impact on public health. Therefore, the objective of our study was to assess any association between Cd exposure and renal cancer risk by conducting cohort, case control, or cross-sectional meta-analysis. In addition, clarifying a relationship might emphasize the importance of considering additional preventative methods for renal cancer. The study was reported following the Preferred Reporting Items for Systematic Reviews14.

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Results

**Literature search, study characteristics, and quality.** Following development of our search strategy, 332 records were initially identified. Thirty-six duplicate studies were excluded; 296 were subsequently screened, and 139 were excluded because titles and abstracts indicated the studies did not fit our criteria. Nineteen full-text articles were reviewed for further assessment. Five articles were excluded because Cd content in kidney tissues was measured\(^{15-19}\), three were not appropriate due to a renal tubular dysfunction outcome\(^{20-22}\), and two were review studies\(^{23,24}\). Finally, nine articles met the meta-analysis criteria and were included (Fig. 1).

The descriptive data for all articles included in the study are summarized in Table 1. One article reported two different ethical approaches, hence it was considered two individual studies\(^10\). Therefore, nine total articles, ten case-control studies (6,013 incident cases and 21,104 controls) and one cohort study (9 renal cancer cases and 1,732 participants) contributed to the meta-analysis. The number of renal cancer patients ranged from 9 to 1,723 across all included studies. The cases were histologically, pathologically, or clinically confirmed as renal cancer. Four studies were based in Europe\(^6,7,10,12\), four in North America\(^5,8,11,13\), and one in a mixed population (Australia, Denmark, Germany, Sweden, and United States)\(^9\). The articles were published from 1976 to 2014. Seven studies were designed to evaluate renal cancer odds ratio (OR)\(^5-8,10,12\), two evaluated relative risk (RR)\(^9,13\), and one evaluated hazard risk (HR)\(^11\). All studies investigated women and men, with the exception of one study, which reported results for the association of renal cancer in men\(^5\). Seven studies adjusted a group of variables for conventional risk factors in renal cancer, including age, gender, geographic area, and smoking\(^8-13\), whereas the other studies did not control for other confounding factors\(^5-7\). Eight studies reported an association between occupational Cd exposure and renal cancer risk\(^5-10,12,13\), while a subject in one study was related to a non-occupational population\(^11\).

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies included in the meta-analysis (Table 2). The median NOS score was 5.7 (range: 4 to 7).

**Overall analysis.** Overall OR estimates for each study were combined to determine total risk estimates using a fixed-effects model (OR = 1.47; 95% CI: 1.27 to 1.71, \(P = 0.000\)) with low heterogeneity (\(I^2 = 0\%\)). Two estimates from the same study were shown; the study provided separate analyses for two case-control studies, which were depicted separately in the figure (Fig. 2).

**Subgroup and sensitivity analysis.** We performed sensitivity analysis to test the stability and robustness of the association, where one study at a time was omitted and the combined OR was computed for the remaining studies. Exclusion of any single study did not notably effect the overall combined OR, which ranged from 1.44 (95% CI: 1.23–1.69) to 1.51 (95% CI: 1.26–1.82); in addition, low heterogeneity was observed. Subgroup analysis was also performed (Fig. 3, Table 3). A statistically significant association between Cd exposure and renal cancer risk was not altered by geographic region and gender; however, mixed results were observed when stratified by sample size, study design, NOS score, adjustment for covariates, effect size, and exposure type. A significant association was found in case-control studies (OR = 1.47, 95% CI: 1.26–1.72), but not in cohort studies (OR = 1.39, 95% CI: 0.43–4.45). When stratified by exposure type, the association was significant between occupational exposure populations (OR = 1.39, 95% CI: 1.26–1.72), but not among non-occupational exposure populations (OR = 1.39, 95% CI: 0.43–4.45). Compared with a low NOS score (OR = 1.23, 95% CI: 0.21–7.11), the association was higher among studies with a high NOS score (OR = 1.46, 95% CI: 1.24–1.71). When stratified by different effects measures, the association was significant among OR studies, but RR or HR risk estimate studies showed a lack of significance. When stratified by sample size, a significant association was detected among studies with patient samples of \(\geq 100\) cases (OR = 1.46, 95% CI: 1.24–1.71), but a significant association was not observed for patient samples of \(< 100\) cases (OR = 1.64, 95% CI: 0.83–3.25).

**Publication bias.** Evidence of publication bias was not detected using Egger’s test (\(P = 0.759\)) and funnel plot symmetry was observed in the meta-analysis (Fig. 4). The results remained unaltered after the trim and fill analysis (OR\(_{\text{fixed}} = 1.47, 95\% \text{CI}: 1.26–1.71; \text{OR}_{\text{random}} = 1.47, 95\% \text{CI}: 1.26–1.71\)), suggesting stable results.)
Cadmium was widely used in industry until one decade ago, when its health risks were recognized, however it is distributed naturally at low levels throughout the environment. Recently, increasing evidence established a link between cadmium exposure and prostate cancer\(^2^5\),\(^2^6\), breast cancer\(^2^7\)–\(^2^9\), pancreatic cancer\(^3^0\),\(^3^1\), and lung cancer\(^3^2\),\(^3^3\). In addition, many current observational studies reported positive associations between exposure to Cd and renal cancer risk. However, these studies had a modest sample size and the association magnitude was variable among studies, with OR ranging from 0.4 (95% CI: 0.05–2.41) to 4.37 (95% CI: 0.44–43.00) and the confidence interval was notably wide. Therefore, the magnitude was limited due to the low precision in risk estimates. These epidemiological studies showed the absence of a comprehensive assessment in cadmium exposure. Therefore, we conducted a comprehensive retrospective meta-analysis to investigate any association between cadmium exposure and renal cancer risk.

### Table 1. Characteristic of studies included in the meta-analysis.

| Study          | Year  | Country          | Study design                     | No. of patients | No. of subjects | Sex | Age, Median (Range), yrs | Exposure type | Study period | Adjustment for covariates                      |
|----------------|-------|------------------|----------------------------------|-----------------|-----------------|-----|-------------------------|---------------|-------------|-----------------------------------------------|
| Kolonel LN     | 1976  | United States    | A case-control study             | 64              | 333             | M   | NA (50-79)              | Occupational exposure | 1957-1964   | Unadjusted                                   |
| Armstrong BG   | 1985  | Britain          | A nested case-control study       | 9               | 36              | M and W | NA (NA)               | Occupational exposure | NA          | Unadjusted                                   |
| Partanen T     | 1991  | Finland          | A case-control study             | 408             | 1227            | M and W | 63 (26-95)             | Occupational exposure | 1977-1978   | Unadjusted                                   |
| McCredie M     | 1993  | United States    | A population based case-control study | 489            | 1012            | W and M | NA (20-79)             | Occupational exposure | 1989-1991   | Adjusted for age, sex, method of interview, and education. |
| Mandel JS      | 1995  | Mixed countries (Australia, Denmark, Germany, Sweden and United States) | A multicenter collaborative case-control study | 1732           | 4041            | M and W | NA (5-68)             | Occupational exposure | 1961-1979   | Adjusted for age, smoking status, heating oils, kerosene, diesel fuel, body-mass index, education and study center. |
| PeschB         | 2000  | German and British | A case-control study             | 935             | 5233            | W and M | NA (40-80)             | Occupational exposure | 1991-1995   | Adjusted for age, study centre, and smoking. |
| Hu J           | 2002  | Canada           | A case-control study             | 1279            | 6649            | W and M | NA (20-70)             | Occupational exposure | 1994-1997   | Adjusted for 10 year age groups, province, education, BMI (<20, 20-27, >27), pack-years of smoking, alcohol use and total consumption of meat. |
| Boffetta P     | 2011  | Europe           | A hospital-based case-control study | 1097           | 2573            | W and M | NA (45-65)             | Occupational exposure | 1993-2003   | Adjusted for gender, age (5-year categories), study centre, and known or suspected risk factors of RCC: place of residence (rural/urban), tobacco smoking (non-smokers, ex-smokers, and current smokers of <1, 1-19, 20-39 and 40 or more pack-years), body mass index (calculated as weight/height 2 and classed in five categories: less than 25, 25-29.4, 29.5-32.9, 30-34.9 and 35 or more kg/m 2) and self-reported history of hypertension. |
| Garcia-Esquilas E | 2014 | United States    | A prospective cohort study       | 25              | 3792            | W and M | 56.2 (45-74)            | Non-polluted exposure | 1989-1991   | Adjusted for sex, age, smoking status (never, former, current), cigarette pack-years (continuous), and BMI (<25, 25–30, ≥30 kg/m2). |

### Table 2. Quality assessment of eligible studies based on Newcastle-Ottawa scale.

| Author          | Year  | Selection | Comparability | Exposure |
|-----------------|-------|-----------|---------------|----------|
| Kolonel LN      | 1976  | 1         | 1             | 2        |
| Armstrong BG    | 1985  | 2         | 1             | 1        |
| Partanen T      | 1991  | 2         | 1             | 2        |
| McCredie M      | 1993  | 2         | 1             | 2        |
| Mandel JS       | 1995  | 2         | 1             | 3        |
| PeschB          | 2000  | 3         | 2             | 2        |
| Hu J            | 2002  | 3         | 1             | 3        |
| Boffetta P      | 2011  | 3         | 1             | 2        |
| Garcia-Esquilas E | 2014 | 3         | 2             | 2        |

**Discussion**

Cadmium was widely used in industry until one decade ago, when its health risks were recognized, however it is distributed naturally at low levels throughout the environment. Recently, increasing evidence established a link between cadmium exposure and prostate cancer\(^2^5\),\(^2^6\), breast cancer\(^2^7\)–\(^2^9\), pancreatic cancer\(^3^0\),\(^3^1\), and lung cancer\(^3^2\),\(^3^3\). In addition, many current observational studies reported positive associations between exposure to Cd and renal cancer risk. However, these studies had a modest sample size and the association magnitude was variable among studies, with OR ranging from 0.4 (95% CI: 0.05–2.41) to 4.37 (95% CI: 0.44–43.00) and the confidence interval was notably wide. Therefore, the magnitude was limited due to the low precision in risk estimates. These epidemiological studies showed the absence of a comprehensive assessment in cadmium exposure. Therefore, we conducted a comprehensive retrospective meta-analysis to investigate any association between cadmium exposure and renal cancer risk.
To the best of our knowledge, this is the first meta-analysis to explore the role of cadmium exposure in renal cancer patients. The overall results of the present meta-analysis of ten observational studies using a fixed-effects model provided evidence that a high Cd exposure was associated with increased renal cancer risk. The pooled estimates were robust across the sensitivity and subgroup analyses, and publication bias was not detected. The conclusions from combined estimates were more reliable than from a single study because the overall OR was based on a large sample size and exhibited sufficient power.
Table 3. Results of overall subgroup analysis. OR, odds ratio; CI, confidence interval; NA, not available; Large, ≥ 100 cases; Small, < 100 cases; High, NOS score of ≥ 5; Low, NOS score of < 5.

|                          | Studies, N | Cases, N | Participants, N | OR (95% CI)   | P-value | P of heterogeneity | F (%) |
|--------------------------|------------|----------|-----------------|---------------|---------|--------------------|-------|
| Total                    | 10         | 6038     | 24896           | 1.47 (1.27–1.71) | 0.000   | 0.807              | 0.0   |

| Geographic region        |            |          |                 |               |         |                    |       |
|--------------------------|------------|----------|-----------------|---------------|---------|--------------------|-------|
| Europe                   | 5          | 2513     | 9402            | 1.42 (1.20–1.70) | 0.000   | 0.596              | 0.0   |
| North America            | 4          | 1793     | 11453           | 1.54 (1.04–2.28) | 0.030   | 0.671              | 0.0   |
| Mixed population         | 1          | 1732     | 4041            | 2.00 (1.01–3.95) | 0.046   | NA                 | NA    |

| Effect size              |            |          |                 |               |         |                    |       |
|--------------------------|------------|----------|-----------------|---------------|---------|--------------------|-------|
| OR                       | 7          | 3792     | 116051          | 1.46 (1.24–1.71) | 0.000   | 0.653              | 0.0   |
| RR                       | 2          | 2221     | 5053            | 1.63 (0.95–2.82) | 0.079   | 0.327              | 0.0   |
| HR                       | 1          | 25       | 3792            | 1.39 (0.43–4.54) | 0.585   | NA                 | NA    |

| Sample size              |            |          |                 |               |         |                    |       |
|--------------------------|------------|----------|-----------------|---------------|---------|--------------------|-------|
| Large                    | 7          | 5940     | 20735           | 1.46 (1.24–1.71) | 0.000   | 0.894              | 0.0   |
| Small                    | 3          | 98       | 4161            | 1.64 (0.83–3.25) | 0.155   | 0.232              | 31.6  |

| Adjustment for covariates|            |          |                 |               |         |                    |       |
|--------------------------|------------|----------|-----------------|---------------|---------|--------------------|-------|
| Yes                      | 7          | 5557     | 23300           | 1.45 (1.23–1.72) | 0.000   | 0.894              | 0.0   |
| NO                       | 3          | 481      | 1596            | 1.57 (1.00–2.47) | 0.050   | 0.230              | 31.9  |

| NOS score                |            |          |                 |               |         |                    |       |
|--------------------------|------------|----------|-----------------|---------------|---------|--------------------|-------|
| High                     | 8          | 5965     | 24527           | 1.46 (1.24–1.71) | 0.000   | 0.943              | 0.0   |
| Low                      | 2          | 73       | 369             | 1.23 (0.21–7.11) | 0.817   | 0.094              | 64.4  |

| Study design             |            |          |                 |               |         |                    |       |
|--------------------------|------------|----------|-----------------|---------------|---------|--------------------|-------|
| Case control study       | 9          | 6013     | 21104           | 1.47 (1.26–1.72) | 0.000   | 0.726              | 0.0   |
| Cohort                   | 1          | 25       | 3793            | 1.39 (0.43–4.54) | 0.585   | NA                 | NA    |

| Exposure type            |            |          |                 |               |         |                    |       |
|--------------------------|------------|----------|-----------------|---------------|---------|--------------------|-------|
| Occupational exposure    | 9          | 6013     | 21104           | 1.47 (1.26–1.72) | 0.000   | 0.726              | 0.0   |
| Non-occupational exposure| 1          | 25       | 3792            | 1.39 (0.43–4.54) | 0.585   | NA                 | NA    |

| Gender                   |            |          |                 |               |         |                    |       |
|--------------------------|------------|----------|-----------------|---------------|---------|--------------------|-------|
| Male                     | 3          | NA       | NA              | 1.40 (1.16–1.69) | 0.001   | 0.740              | 0.0   |
| Female                   | 3          | NA       | NA              | 1.64 (1.09–2.47) | 0.019   | 0.243              | 29.3  |

Figure 4. Funnel plot for publication bias analysis results.
Several mechanisms are responsible for the carcinogenesis of Cd exposure. Recently, several observational studies using in vitro cell culture and in vivo animal studies demonstrated a proliferative and carcinogenic effect of Cd on various cancers34–36. A major portion of Cd is bound to metallothionein proteins. These proteins, which have low molecular weight, play a vital role in essential-metal homeostasis37. The cadmium-metallothionein compound is disseminated in different organs and subsequently reabsorbed in kidney tubules. A Cd excretion mechanism is not present in the human body, resulting in Cd accumulation. Cadmium half-life in the human kidney cortex is ∼10–30 years38. Proto-oncogene activation, tumor suppressor gene inactivation, cell adhesion disruption, and DNA mismatch repair inhibition are some cellular and molecular mechanisms indicated in cadmium carcinogenicity39–41. These processes are involved in cancer development.

The present meta-analysis exhibited several strengths. First, the meta-analysis was the first to investigate an association between Cd exposure and renal cancer risk. Second, the large sample size improved the risk estimate accuracy and resulted in well-founded conclusions based on the meta-analysis. Third, the analysis employed multivariable-adjusted risk estimates to minimize the confounding factors that influenced Cd exposure levels. The studies with adjusted risk estimates accurately reflected the association between Cd exposure level and renal cancer risk. Fourth, low heterogeneity was detected across the studies and publication bias was not observed.

Nevertheless, some limitations should be considered in the present meta-analysis. First, although a case-control study is the most appropriate design for toxicity exposure (e.g., occupational or environmental) causing rare health events, this design has inherent limitations, such as selective and recall or memory bias. Second, confounding factors, including co-exposure to other toxic chemicals and lifestyle factors (e.g., lead, asbestos, arsenic, tobacco and/or alcohol consumption) are difficult to control in a meta-analysis. Third, the small number of studies included in a meta-analysis limits the ability to draw robust conclusions, particularly in the subgroup analysis. Finally, the included studies were only distributed in Europe and North America. Therefore, further study should investigate the association between Cd exposure and renal cancer susceptibility among Caucasian, African, and Asian populations or additional ethnicities on other continents.

The following factors should be considered for further studies. First, in the meta-analysis, we found only one study validated Cd exposure levels. It is vital to estimate Cd exposure levels in urine and blood, proportional to the body’s tolerance, which reflect long-term Cd exposure levels. The precision of observational Cd related renal cancer hypothesis studies could be greatly improved by incorporating Cd exposure biomarkers. Therefore, future studies should examine Cd levels in urine and blood as a method to assess long-term Cd exposure. Second, most studies we examined investigated the association between Cd occupational exposure and renal cancer risk. Therefore, the results of our meta-analysis should only be used to infer Cd under occupational conditions leading to increased renal cancer risk. Compared with the general population, Cd levels are typically higher in certain industries as a component of an occupational population where Cd is present (e.g., nickel batteries, pigments, and soldering alloys). However, Cd exposure levels in the general population are usually low. Therefore, further studies are needed to confirm the association among the non-occupational (Cd-exposed) population. Finally, studies we analyzed in the meta-analysis did not examine whether an association between Cd exposure and renal cancer risk differed among anatomical or histological sub-sites within the body.

In summary, the meta-analysis suggests that a high cadmium exposure may be a risk factor for renal cancer in occupational population. Further study should be conducted to determine whether a low level Cd exposure in general population was associated with increased risk of renal cancer.

Methods

Data source and search strategy. A comprehensive search was performed using PubMed and EMBASE databases to retrieve all potentially related studies up to June 2015. We employed the following search strategies (i.e., search terms) without limitations: “renal cancer” or “kidney cancer” or “renal cell cancer” or “renal cell carcinoma” combined with “cadmium”. The search was limited to human subjects. The previous review and related article references were manually screened to identify other potentially eligible studies.

Eligibility criteria and study selection. Studies were considered eligible for inclusion in the meta-analysis if they met the following criteria: (1) Cd was the heavy metal of human exposure; (2) the outcome was renal cancer risk; (3) the study design was cohort, case control, or cross-sectional; and (4) the relative risk (RR), odds ratio (OR), or hazard risk (HR) with corresponding 95% confidence interval (CI) were reported or provided sufficient data to estimate crude OR, RR, or HR with corresponding 95% CI. If the included population was duplicated in more than one study, only data from the study with the most comprehensive information was included.

Data extraction and quality assessment. Two authors (JKS and XHY) independently extracted data from the selected studies. The following key points were collected: first author; publication year; study design; country; total number of cases and subjects; sex; Cd exposure type; and adjusted variables. Adjusted OR was extracted as a preference to non-adjusted OR; however, unadjusted OR and CI were calculated when OR was not provided. When more than one adjusted OR was reported, the ratio with the most number of adjusted variables was selected. Disagreements between authors (JKS and XHY) were resolved through discussion and consensus.

The Newcastle-Ottawa Scale (NOS) was employed to evaluate the methodological quality of each study42. The following three primary components were evaluated and assigned a numerical score: (1) study group selection (0–4 points); (2) determination of the exposure source in the study (0–3 points); and (3) adjustment parameters for confounding factors (0–2 points). The total score was nine; a high-quality study was defined as ≥5.

Statistical analysis. We used OR with 95% CI as the common measure across all studies. Cd caused renal cancer was considered a rare event, the RR and HR in the cohort study was considered approximations of OR. Two
articles did not report overall risk estimates, but instead separately presented results for men and women. Therefore, we combined the results using fixed effects and included the pooled risk estimates in the primary analysis. The OR in two studies failed to extract, so we computed the crude risk estimates and corresponding CI. The summary risk estimates were calculated using random- or fixed-effects models as appropriate based on heterogeneity levels. Heterogeneity among studies was assessed using the I² statistic, which measured quantitative inconsistency in heterogeneity levels across studies. Studies with I² values from 25% to 50% exhibited low heterogeneity, 50% to 75% showed moderate heterogeneity, and studies with results >75% exhibited high heterogeneity. An I² value >50% and \( \text{I}^2 \text{heterogeneity} < 0.10 \) indicated significant heterogeneity. Sensitivity analysis was conducted to evaluate data robustness and stability by sequentially omitting one study on each turn. Studies were sequentially omitted if the data did not meet the restrictions. In addition, subgroup analysis was stratified by study design, effects measure, geographic region, sample size, exposure type, adjustment for variates, and NOS quality.

We evaluated potential publication bias using a funnel plot and Egger's tests, with a priori \( P < 0.1 \) indicating a significant publication. If asymmetry evidence was detected, the trim and fill method was employed to correct publication bias. All statistical analyses were conducted using Stata version 13.1 (Stata Corp, College Station, TX, USA).

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J.K.S., G.L.H., X.H.Y., S.Y.L., J.G.Z. and W.Z. wrote the main manuscript text; J.K.S., G.L.H., X.H.Y., D.R.L., K.Z., H.L. and D.P.Y. prepared Figures 1–4; J.K.S. G.L.H. and J.G.Z. contributed data analysis;

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