



Association between cadmium exposure and risk of endometrial cancer; a systematic review and meta-analysis of clinical trial and observational studies

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Abstract

Introduction: Endometrial cancer is the most prevalent cancer in women, and heavy metals, including cadmium, are among the factors associated with cancer development. Therefore, this study aimed to investigate the relationship between cadmium exposure and the risk of endometrial cancer using a systematic review and meta-analysis.

Materials and Methods: In this systematic review and meta-analysis, which was conducted by the PRISMA guidelines, several databases, including PubMed, Scopus, Web of Science, Cochrane, and Google Scholar search engine, were searched without time restrictions until August 8, 2023. Data analysis was performed using STATA 14 software, and statistical significance was considered at $P < 0.05$.

Results: The results of the analysis of six studies involving a total of 160,043 women (2282 in the case group and 157,761 in the control group) showed that cadmium exposure had no significant effect on the risk of endometrial cancer development (OR: 1.02, 95% CI: 0.92–1.13). Furthermore, there was no statistically significant association between menopause and the risk of endometrial cancer development (OR: 3.91, 95% CI: 0.50–30.73). Additionally, there was no statistically significant association between body mass index >25 kg/m² and the risk of endometrial cancer development (OR: 1.04, 95% CI: 0.86–1.26), with smoking and the risk of endometrial cancer development (OR: 0.91, 95% CI: 0.61–1.36) too. Furthermore, there was no statistically significant association between hormone therapy and the risk of endometrial cancer development (OR: 0.81, 95% CI: 0.63–1.04) as well.

Conclusion: Our study demonstrated that cadmium exposure is not associated with an increased risk of endometrial cancer. However, further research in this area is recommended due to the limited number of studies available.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42023462640).



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Introduction

The International Agency for Research on Cancer (IARC) has classified cadmium as a group 1A carcinogen (1). Cadmium levels in adults are usually less than 0.5 micrograms per 100 milliliters of blood (2). The primary environmental source of cadmium in non-smokers who are not occupationally exposed to cadmium is the diet (3). It has been reported that over 80% of dietary cadmium comes from grains and vegetables (4). The average daily cadmium intake from food varies from 8 to 25 mg (5). Smoking is a significant source of cadmium exposure, as cadmium readily accumulates in tobacco plants, and cadmium in tobacco smoke is efficiently absorbed

in the lungs (5). Additionally, low iron status increases cadmium absorption in the intestine, leading to higher cadmium levels in women compared to men (6,7). Endometrial cancer (EC) is the most common cancer in women, and its incidence is increasing (8). Several risk factors for endometrial cancer exist, including high blood pressure, diabetes, and conditions related to excessive estrogen exposure, such as early menstruation, late menopause, and a high body mass index (9). Other recognized risk factors for endometrial cancer include hormone replacement therapy (HRT), lower physical activity, and a family history of the disease (10,11).

Key point

Heavy metals, including cadmium, are among the factors associated with cancer development. Endometrial cancer is the most prevalent cancer in women and in this study investigated the relationship between cadmium exposure and the risk of endometrial cancer, and demonstrated that exposure to cadmium does not significantly impact the incidence of endometrial cancer. Factors such as smoking, hormone therapy, menopause, and body mass index >25 kg/m² in women do not increase the risk of endometrial cancer. It is recommended that more research be conducted in the future to provide greater confidence in the relationship between cadmium and endometrial cancer.

Experimental studies using in vitro cell culture and in vivo animal studies have shown that exposure to cadmium can lead to cellular transformation and induce cancer in various organs (12). Although existing data, especially for endometrial cancer, is insufficient, hormone-related cancers may be more susceptible to estrogen-mimicking substances like cadmium (13). Given the conflicting results of previous studies (13,14), the present study was conducted for the first time to systematically investigate the association between cadmium and endometrial cancer using a systematic review and meta-analysis.

Materials and Methods

The present research was a systematic review and meta-analysis designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15), and its protocol is registered on the International Prospective Register of Systematic Reviews (PROSPERO) website (ID: CRD42023462640).

Search strategy

In this study, the international databases PubMed, Scopus, Web of Science, Cochrane, and Google Scholar search engine were searched without time restrictions until August 8, 2023. The search was conducted using standard keywords and Medical Subject Headings (Mesh), including Cadmium, Endometrial Neoplasms, Endometrial Carcinoma, and Endometrium Cancers. Keyword combinations were searched using Boolean operators (AND, OR) in the mentioned databases. To perform a manual search, a list of relevant primary studies was searched. A sample of the search strategy used in PubMed is as follows: (Endometrial Neoplasms OR Endometrial Carcinoma OR Endometrium Cancers) AND (Cadmium).

PICO components

- Population: cohort studies, case-control studies, and clinical trials that evaluated the relationship between cadmium and endometrial cancer.
- Intervention: Cadmium exposure.
- Comparison: Women not exposed to cadmium.
- Outcomes: risk of developing endometrial cancer as

measured by relative risk (RR), odds ratio (OR), and hazard ratio (HR).

Study exclusion criteria

Case report studies, descriptive studies, having no access to some articles' full-text, protocol papers, editorials, studies with low methodological quality, studies without necessary data for analysis, and duplicate studies were excluded.

Quality assessment of primary studies

After identifying the primarily included studies, two reviewers independently assessed the quality of clinical trial studies using the Cochrane Collaboration's Checklist for Assessing Risk of Bias in Randomized Trials (16). This checklist comprises seven questions, each of which evaluates one of the important types of bias in clinical trials. Each question has three response options; high risk of bias, low risk of bias, and unclear risk of bias. To assess the quality of observational studies, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used (17). This checklist comprises 22 questions, and the total score ranges from 0 to 44. Studies scoring less than 12 were considered low-quality and were excluded. After completing the assessment of bias in the studies, discrepancies in responses to the checklist questions in each study were first evaluated. By reaching a consensus or agreement between the two assessors, these discrepancies were then resolved and converted into a single unified response.

Data extraction

Two researchers independently conducted data extraction from the studies. The researchers entered the extracted data into a checklist, which included the following items: first author's name, publication year of the study, number of women, country, study type, age, cadmium levels, relative risk of the relationship between cadmium exposure and endometrial cancer, along with the 95% confidence interval. A third researcher reviewed the extracted data from the two previous researchers to resolve any discrepancies if they existed.

Statistical analysis

The studies' results reported using the RR, OR, or HR indices were combined. OR was conducted as a representative index for assessing the association between cadmium and endometrial cancer. The logarithm of OR was calculated for each study and used for combining the study results. To assess heterogeneity, the Q Cochrane test and calculation of the I² index were employed. Meta-regression was used to investigate the reasons for heterogeneity, and a funnel plot was used to assess publication bias (18). The I² index is classified into three categories; less than 25% indicates low heterogeneity, between 25% and 75% indicates moderate

heterogeneity, and greater than 75% indicates severe heterogeneity (19). In the current study, a random-effects model was utilized. Data analysis was performed using STATA 14 software, and a significance level of $P < 0.05$ was considered.

Results

Study selection

Initially, a total of 104 articles were found through the mentioned database search. After reviewing the titles of the studies, 36 duplicate studies were excluded. The abstracts of the remaining 68 articles were reviewed, and out of these, six articles were excluded due to the unavailability of their full texts. Among the remaining 62 articles, five articles were excluded due to incomplete required information, leaving 57 articles. Finally, 51 more articles were excluded based on other exclusion criteria, resulting in six articles entering the systematic review and meta-analysis process (Figure 1).

In six studies examined, a total of 160,043 women (2282 in the case group and 157,761 in the control group) were evaluated. The average age of individuals in the case and control groups ranged from 50 to 79 years. The extent of cadmium exposure varied across different studies (Table 1).

Primary Outcome

Figure 2 indicates that there is no statistically significant association between exposure to cadmium and the risk of endometrial cancer (OR: 1.02, 95% CI: 0.92–1.13).

Secondary outcomes (examination of endometrial cancer risk factors)

There is no statistically significant association between menopause in women and the risk of endometrial cancer (OR: 3.91, 95% CI: 0.50–30.73) (Figure 3).

Moreover, women with a body mass index (BMI) >25 kg/m² did not experience an increased risk of endometrial cancer (OR: 1.04, 95% CI: 0.86–1.26) (Figure 4).

Figure 5 shows that smoking in women does not significantly impact their susceptibility to endometrial cancer (OR: 0.91, 95% CI: 0.61–1.36).

Figure 6 illustrates that there is no statistically significant association between hormone therapy and the risk of endometrial cancer (OR: 0.81, 95% CI: 0.63–1.04).

Additional analysis

Meta regression analysis demonstrates that there is no statistically significant relationship between “exposure to cadmium and the risk of endometrial cancer” and the year of study ($P = 0.603$). In other words, exposure to cadmium

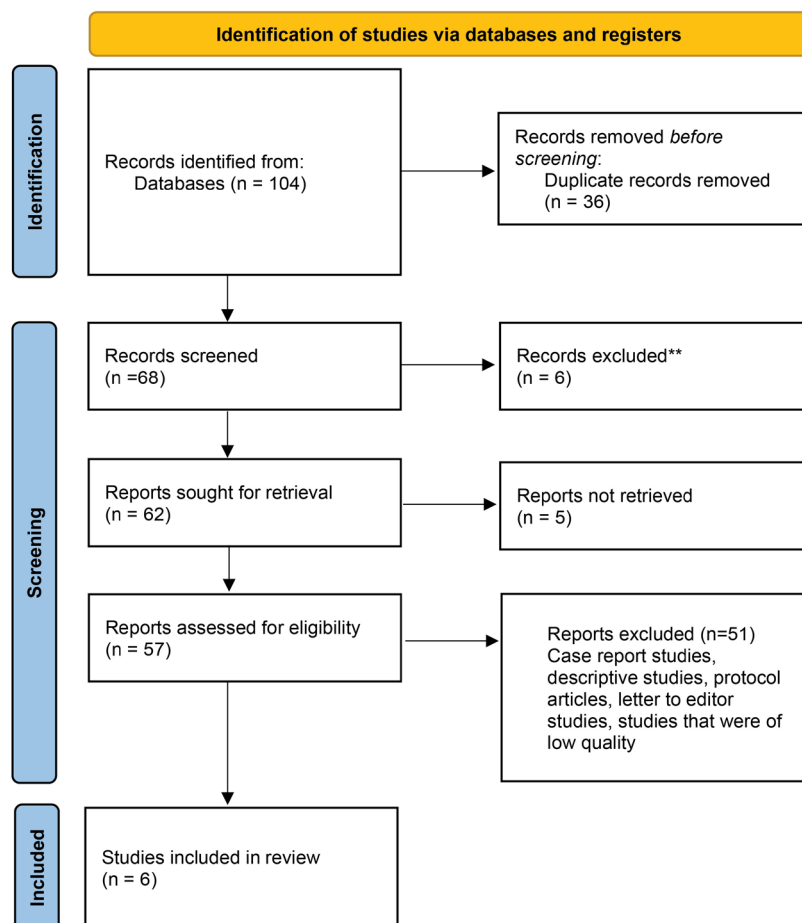


Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Summary of the information available in the reviewed articles

Author, year of publication	Country	Type of study	Number of people in case group	Meam age in case group	Number of people in control group	Meam age in control group	Compared with	During the study period	Cadmium intake
Michalczyk K, 2023 (20)	Poland	Clinical trial	21	52	89	52	Endometrial polyps, endometrial hyperplasia, uterine myoma, and normal endometrium	9-Mar-20	Upper quartile
Michalczyk K, 2023 (20)	Poland	Clinical trial	21	52	89	52	Endometrial polyps, endometrial hyperplasia, uterine myoma, and normal endometrium	9-Mar-20	Median
Michalczyk K, 2023 (20)	Poland	Clinical trial	21	52	89	52	Endometrial polyps, endometrial hyperplasia, uterine myoma, and normal endometrium	9-Mar-20	Lower quartile
McElroy JA, 2017 (13)	USA	Case-control	631	60.1	879	62.9	Women age-matched	from Jan 2010 to Oct 2012	NR
Adams SV, 2014 (14)	USA	Clinical trial	289	50-79	18338	50-79	Postmenopausal women	through Aug 2009	> 14.21 µg
Adams SV, 2014 (14)	USA	Clinical trial	289	50-79	18338	50-79	Postmenopausal women	through Aug 2009	11.35–14.21 µg
Adams SV, 2014 (14)	USA	Clinical trial	289	50-79	18338	50-79	Postmenopausal women	through Aug 2009	9.24–11.35 µg
Adams SV, 2014 (14)	USA	Clinical trial	289	50-79	18338	50-79	Postmenopausal women	through Aug 2009	7.10–9.24 µg
Eriksen KT, 2014 (21)	Denmark	Cohort	192	50-65	23623	50-65	Postmenopausal women	through Dec 31, 2010	10 mg
Eriksen KT, 2014 (21)	Denmark	Cohort	192	50-65	23623	50-65	Postmenopausal women	through Dec 31, 2010	11.9–15.3 µg
Eriksen KT, 2014 (21)	Denmark	Cohort	192	50-65	23623	50-65	Postmenopausal women	through Dec 31, 2010	>15.3 µg
Akesson A, 2008 (22)	Sweden	Cohort	151	61.6	29832	61	Postmenopausal women	between the baseline and mid-2006	>16.0 µg
Akesson A, 2008 (22)	Sweden	Cohort	111	61	NR	61	NR	NR	13.7–16.0 µg
Rull R, 2014 (23)	USA	Cohort	887	NR	85000	NR	Teachers	between 1996 and 2010	NR

NR: Not reported.

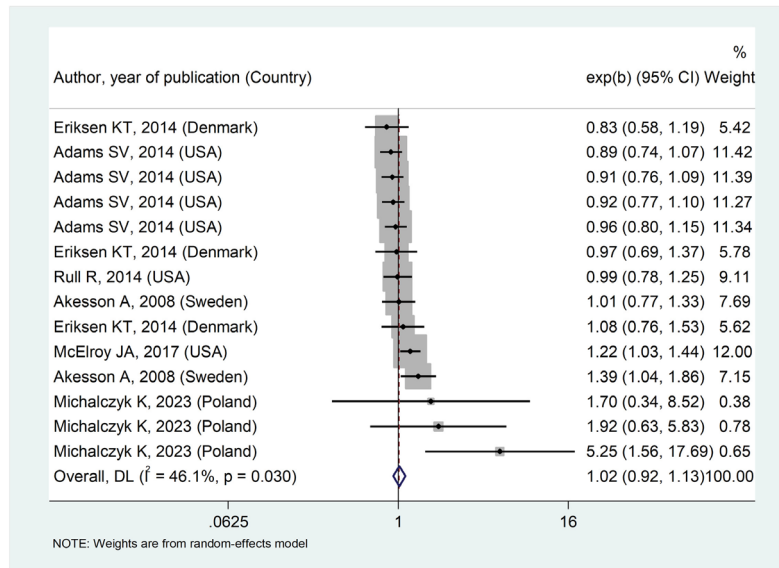


Figure 2. Forest plot of the association between cadmium exposure and risk of endometrial cancer with its 95% confidence interval.

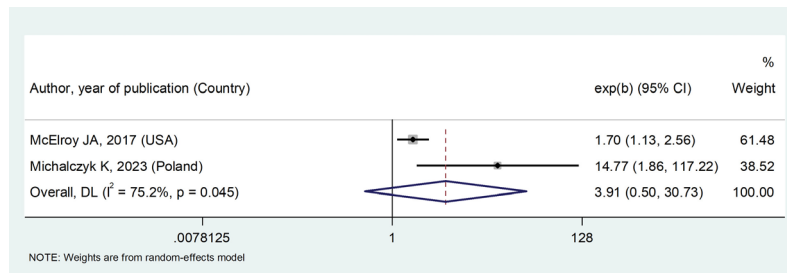


Figure 3. Forest plot of the association between cadmium exposure and risk of endometrial cancer in menopausal women with its 95% confidence interval.

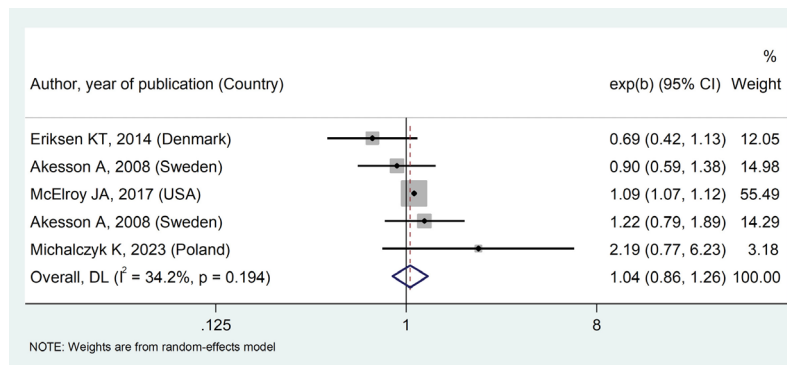


Figure 4. Forest plot of the association between cadmium exposure and risk of endometrial cancer in women BMI > 25 kg/m² with its 95% confidence interval.

did not lead to a statistically significant change in the trend of endometrial cancer incidence during the years from 2008 to 2023 (Figure 7).

Meta regression analysis also shows that there is no statistically significant relationship between “exposure to cadmium and the risk of endometrial cancer” and the sample size of the studies ($P = 0.975$). This means that it is not the case that in larger studies (those with a larger sample size), exposure to cadmium increased the risk of

endometrial cancer, and in smaller studies (those with a smaller sample size), exposure to cadmium reported a lower risk of endometrial cancer (Figure 8).

The statistical significance of publication bias analysis was not observed in the publication bias funnel plot ($P=0.083$), indicating that the literature search phase was conducted thoroughly. Studies reporting exposure to cadmium as a risk factor for endometrial cancer and those reporting it as having no effect on endometrial cancer

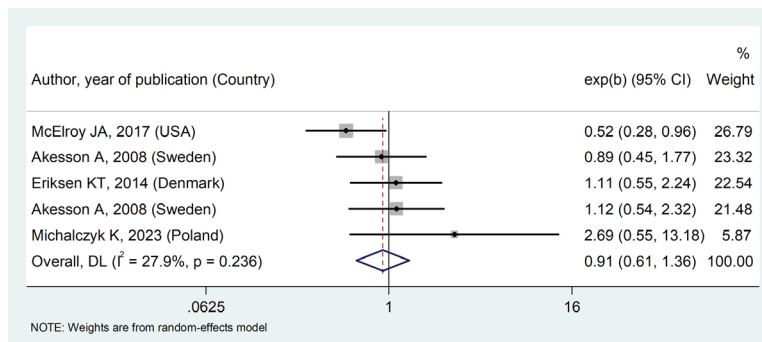


Figure 5. Forest plot of the association between cadmium exposure and risk of endometrial cancer in Smoking women with its 95% confidence interval.

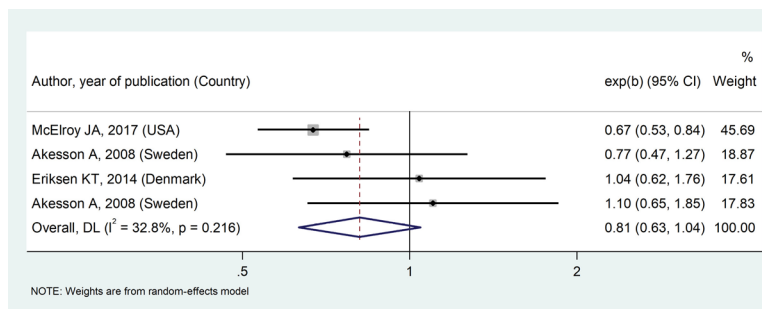


Figure 6. Forest plot of the association between cadmium exposure and risk of endometrial cancer in Women undergoing hormone replacement therapy with its 95% confidence interval.

risk all had an equal chance of being published and were included in our search, with no evidence of publication bias (Figure 9).

Discussion

The results of this meta-analysis showed that exposure to cadmium does not have a significant impact on the risk of endometrial cancer. In a meta-analysis by Flórez-García and colleagues based on 17 studies, they demonstrated an increased risk of breast cancer in women exposed to higher levels of cadmium (OR: 1.13 (95% CI: 1.00, 1.28)). However, exposure to cadmium through diet did not

increase the risk of breast cancer in women (OR: 1.05; 95% CI: 0.91, 1.21), and no clear pattern of risks based on menopausal status was observed (24). In the current meta-analysis, there was no statistically significant association between menopausal status in women and the risk of endometrial cancer. It should be noted that since only two studies (13, 20) have examined this relationship, it is possible that the association between menopause and the occurrence of endometrial cancer did not reach statistical significance.

In a cohort study by Julin and colleagues, which included 60,889 women and was conducted in Sweden, no

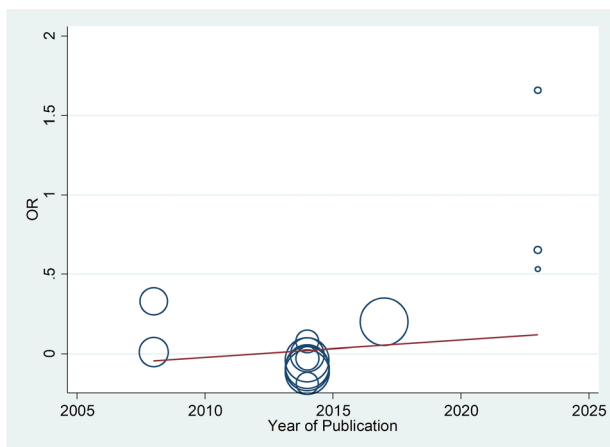


Figure 7. Meta-regression plot of association between “cadmium exposure and risk of endometrial cancer” by year of publication studies.

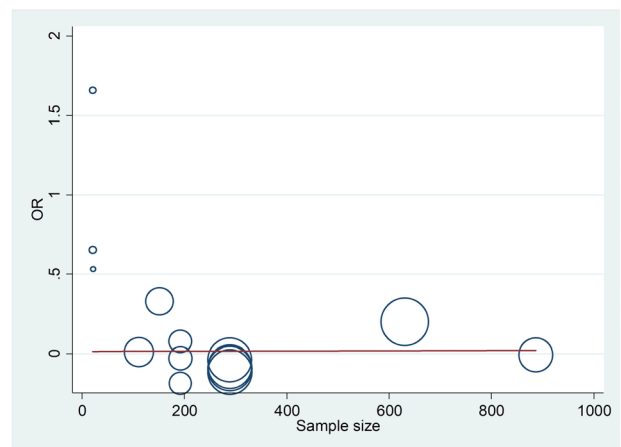


Figure 8. Meta-regression plot of association between “cadmium exposure and risk of endometrial cancer” by sample size of studies.

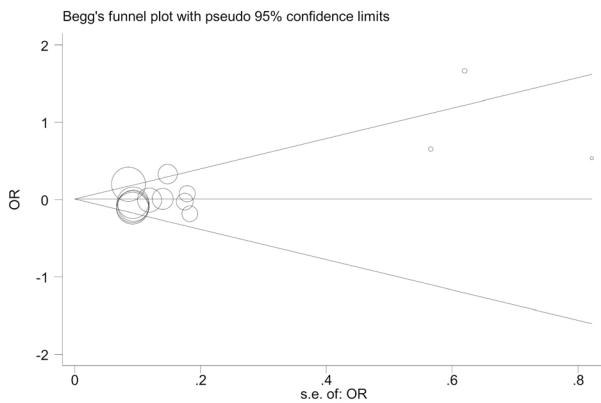


Figure 9. Publication bias.

association was reported between exposure to cadmium through diet and the risk of epithelial ovarian cancer (RR: 0.90; 95% CI: 0.71–1.15) (25). The results of a meta-analysis by Filippini and colleagues, which included ten studies to investigate the relationship between exposure to cadmium and the incidence of breast cancer and mortality in cohort studies revealed that, in comparison to non-exposure to cadmium, the likelihood of developing breast cancer for a daily exposure of 20 μg of cadmium was (RR: 1.12; 95% CI: 0.80–1.56), and for 2 μg , it was (RR: 0.89; 95% CI: 0.38–2.14). Both of these relationships were not statistically significant (26). In an analysis conducted by Chen and colleagues, the association between exposure to cadmium and the relative risk of lung cancer in the general population was reported as (RR: 1.42; 95% CI: 0.91, 2.23), which was not statistically significant (27). The meta-analysis by Ju-Kun and colleagues showed that in the general population, exposure to a large amount of cadmium did not have a significant relationship with an increased risk of prostate cancer (OR 1.21; 95% CI 0.91–1.64) (28). These studies have shown that there is no statistically significant association between exposure to cadmium and the occurrence of epithelial ovarian, breast, lung, and prostate cancers. These results are consistent with the findings of the current meta-analysis, as we also concluded that exposure to cadmium is not significantly associated with endometrial cancer.

Differences in body cadmium levels, duration of cadmium exposure, and the manner of cadmium exposure (occupational, dietary, smoking, etc) in the studies under investigation are among factors that may have introduced heterogeneity, ultimately rendering the relationship between cadmium exposure and cancer incidence statistically insignificant.

According to the results of the recent meta-analysis by Zhang et al, which included 14 studies aimed at examining the relationship between cadmium levels and the risk of liver cancer, it was found that cadmium levels in patients with liver cancer were significantly higher than in healthy individuals (standard mean difference: 2.00; 95% CI: 1.20–

2.81; $P < 0.05$) (29). In a meta-analysis conducted by Chen et al comprising 6 observational studies, researchers found that cadmium exposure increased the risk of pancreatic cancer (RR: 2.05; 95% CI: 1.58–2.66) (30). In a meta-analysis by Song et al, exposure to high levels of cadmium was associated with an increased risk of kidney cancer (OR: 1.47; 95% CI: 1.27 to 1.71) (31). Based on these studies, it is evident that exposure to cadmium and the subsequent elevation of cadmium levels in the body increase the risk of kidney, liver, and pancreatic cancers. However, it should be noted that our meta-analysis examined endometrial cancer, which is common in women, while the studies (29–31) assessed both women and men together. Furthermore, cadmium accumulates predominantly in the kidneys and liver in the human body, possibly due to the kidneys and liver's ability to synthesize metallothionein. This may be a reason for the reported significant associations between cadmium and cancers such as kidney and liver (32,33), which could explain the lack of consistency between the current study's results and those of other studies (29–31).

The strength of our study is that it is the first meta-analysis to investigate the relationship between cadmium exposure and the risk of endometrial cancer. However, it has limitations, including (a) the inability to assess the relationship between cadmium exposure and endometrial cancer risk based on age groups of women; (b) the inability to compare the relationship between cadmium exposure and endometrial cancer risk within subgroups based on the duration of cadmium exposure; (c) the inability to evaluate the association between cadmium exposure and endometrial cancer risk based on the amount of cadmium intake due to the lack of distinguishable and categorized cadmium amounts; considering the amount of cadmium introduced into the body does play a significant role in cancer development; and 4) due to the limited number of studies investigated and the diversity of study types, the possibility of analyzing results based on study type was not feasible. It is hoped that future studies will address these limitations.

Conclusion

This meta-analysis demonstrated that exposure to cadmium does not significantly impact the incidence of endometrial cancer. Factors such as smoking, hormone therapy, menopause, and BMI $> 25 \text{ kg/m}^2$ in women do not increase the risk of endometrial cancer. Given the limited number of studies examined, it is recommended that more research be conducted in the future to provide greater confidence in the relationship between cadmium and endometrial cancer and to allow for more generalizable results.

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Authors' contribution

Conceptualization: Elham Saffarieh, Setare Nassiri and Seyedeh Reyhaneh Yousefi Sharemi.

Data curation: Setare Nassiri.

Formal analysis: Setare Nassiri.

Funding acquisition: Elham Saffarieh and Seyedeh Reyhaneh Yousefi Sharemi.

Investigation: Elham Saffarieh.

Methodology: Azadeh Yousefnezhad, Setare Nassiri and Fahimeh Nokhostin.

Project administration: Elham Saffarieh and Fahimeh Nokhostin.

Resources: Elham Saffarieh, Azadeh Yousefnezhad and Fahimeh Nokhostin.

Supervision: Setare Nassiri

Validation: Seyedeh Reyhaneh Yousefi Sharemi.

Visualization: Elham Saffarieh and Seyedeh Reyhaneh Yousefi Sharemi.

Writing-original draft: Seyedeh Reyhaneh Yousefi Sharemi.

Writing-review and editing: Elham Saffarieh, Azadeh Yousefnezhad and Fahimeh Nokhostin.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website with (ID: [CRD42023462640](https://doi.org/10.1186/CRD42023462640)). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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