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Cadmium Exposure and Risk of Pancreatic Cancer: A Systematic Review and Meta-Analysis

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Abstract

Introduction: *Pancreatic cancer is a highly lethal malignancy with poor prognosis and limited treatment options. Environmental exposures, particularly to heavy metals such as cadmium, may contribute to its etiology. This systematic review and meta-analysis evaluated the association between cadmium exposure from different sources and pancreatic cancer incidence or mortality.* **Methods:** *Following PRISMA guidelines, we searched PubMed, EMBASE, and Scopus. Eighteen studies comprising 20 risk estimates were included. Random-effects meta-analyses were conducted overall and stratified by exposure source, gender, region, study design, and outcome. Dose-response relationships were assessed using meta-regression of cadmium exposure measures. Publication bias was evaluated using funnel plots and Egger's test.* **Results:** *Overall, cadmium exposure was associated with an increased risk of pancreatic cancer [relative risk (RR) = 1.69, 95% confidence interval (CI): 1.28-2.22]. Occupational exposure showed the most consistent association (RR = 1.38, 95% CI: 1.19-1.61), followed by urinary and blood/serum biomarkers. Risk was higher in men than in women, and in case-control than in cohort studies. Dose-response analysis did not reveal a linear trend. There was limited evidence of publication bias overall, though some asymmetry was observed for urinary cadmium studies (p = 0.045).* **Conclusion:** *Cadmium exposure was associated with pancreatic cancer risk, particularly in occupational and biomarker-based studies. While findings support a potential causal link, heterogeneity, residual confounding, and limited dose-response data necessitate cautious interpretation.*

1. Introduction

Pancreatic cancer is one of the most lethal forms of cancer; it ranks globally as the seventh most common cause of cancer-related death in both men and women. Incidence rates are four to five times higher in countries with a high Human Development Index (HDI), with the greatest burden observed in Europe, North America, and Australia/New Zealand [1, 2]. Despite advances in diagnostics and therapeutics, its prognosis remains poor, with a five-year survival rate lower than 10%, mainly because this type of cancer is frequently detected at an advanced stage [3].

The etiology of pancreatic cancer is multifactorial, involving genetic susceptibility and other risk factors. including tobacco smoking, smokeless tobacco use, excess body weight, high alcohol consumption,

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and exposure to environmental pollutants [4]. Among environmental contributors, some research supports the role of environmental chemicals and heavy metals in the etiology of pancreatic cancer [5]. Heavy metal poisoning traditionally occurred in industrial settings and manifested with severe and overt clinical signs and symptoms; however, such cases are now uncommon. The development of more sensitive diagnostic techniques and biomarkers of toxicity has increased awareness of the health consequences of chronic environmental (non-industrial) exposure to heavy metals [6].

Cadmium (Cd) is a naturally occurring metal that is present in a variety of products and environmental settings [7]. It is a non-essential element with well-established toxicity in humans, with lung cancer being the only neoplasm causally associated with it [8]. Human exposure to cadmium occurs through various sources, including industrial processes and occupational settings such as battery manufacturing, metal plating, coating, pigment production, stabilizer use, and welding. Cadmium contamination of soil, air, and water is widespread due to its use in industrial products, contamination from phosphate fertilizers, and emissions from motor vehicle fuel combustion and tire wear [9, 10]. Additionally, cigarette smoking represents a significant source of exposure, while contaminated food - particularly leafy vegetables, cereals, and shellfish - is the primary source of cadmium intake in non-smokers [11, 12].

Cadmium can accumulate in the body over time, primarily in the liver and kidneys, but it may also affect the pancreas via systemic circulation and oxidative stress. Metal can interfere with cellular signaling pathways, induce chronic inflammation, promote DNA damage, and inhibit DNA repair mechanisms – all of which are hallmarks of cancer development [13, 14].

Understanding the potential link between cadmium exposure and pancreatic carcinogenesis is crucial for public health and may offer insights into preventive strategies and regulatory policies. We conducted a systematic review and meta-analysis of published cohort, nested case-control, and case-control studies to evaluate the association between cadmium exposure and pancreatic cancer risk.

2. Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Tables S1a and S1b) [15]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), Registration number: CRD420251106774.

2.1. Study Design and Criteria

A comprehensive literature search was conducted in MEDLINE (PubMed), EMBASE (Ovid), and SCOPUS in July 2025, with no language restrictions. The study population included adults from all countries on the incidence or mortality of pancreatic cancer, as an outcome without restriction by publication year. For the search strategy, vocabulary terms and keywords related to cadmium exposure, cancer, and pancreatic neoplasms were combined (see Supplementary Table 2 for detailed search strategies used across the various databases). References of included articles and relevant reviews were handsearched to identify additional eligible studies.

We included observational studies (cohort, nested case-control, or case-control) that evaluated the association between cadmium exposure and pancreatic cancer risk. Eligible studies assessed cadmium exposure from environmental, occupational, or biological sources, including measurements in urine, blood, serum, plasma, or toenails, and reported effect estimates for pancreatic cancer incidence or mortality.

Studies were excluded if they: (i) Did not evaluate pancreatic cancer as an outcome, (ii) Did not assess cadmium exposure or failed to report cadmium specific effect estimates, (iii) Were based on occupational groups in which cadmium was not the primary exposure and cadmium-specific results could not be separated such as firefighters, uranium miners, textile workers, printing workers, chimney sweeps, shipyard or pipe trades workers, and ferromanganese plant workers, (iv) Consisted of abstracts, unpublished reports, theses, book chapters, non-peer-reviewed publications or study designs other than cohort and case control, (v) Duplicated

other reports or analyzed overlapping populations (in such cases only the most recent and comprehensive publications were included; see Supplementary Figure 1).

2.2. Study Selection, Data Extraction, and Quality Assessment

All records were uploaded into the online software, Rayyan, where duplicates were removed. Two reviewers independently screened titles and abstracts for potential relevance. The full texts of potentially eligible articles were independently assessed. Any disagreements at any stage of the review process were resolved by discussion. Two reviewers independently extracted the data using a standardized Excel form. Extracted information included study characteristics (authors, year of publication, country, study design), population details, sample size, source and method of cadmium exposure assessment, outcome definition (mortality, incidence), duration and level of exposure, and reported effect estimates [adjusted or unadjusted relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs)] and adjustment list if available. Stratified results (e.g., by gender, age, exposure source, or exposure level) were recorded as separate entries.

The methodological quality of included studies was independently assessed by two reviewers using a modified Newcastle-Ottawa Scale (NOS) [16]. NOS evaluates study characteristics across three main domains: selection of participants, comparability of study groups, and ascertainment of either exposure or outcome. The maximum score was 9 for case-control studies and 10 for cohort studies, with higher scores indicating better quality. See Supplementary Table 3 for details of items for each study type, and the summarized results are presented in Supplementary Table 4.

2.3. Statistical Analysis

Random-effects meta-analyses were conducted to calculate pooled relative risks (RRs) and 95% confidence intervals (CIs), both overall and stratified by source of cadmium exposure (occupational, serum/blood, urine, and others), using the DerSimonian and Laird and the restricted maximum-likelihood (REML) methods [17]. Statistical heterogeneity was assessed using Cochran's Q test and quantified with the I^2 statistic [18]. Because pancreatic cancer is a rare outcome, ORs, HRs, SMRs, and SIRs were considered approximations of RR [19].

Subgroup analyses were performed by gender (male, female, both), study design (cohort, case-control), outcomes (incidence, mortality), region (North America, Europe, other countries), years of publication (<2011 vs. >2011, based on the median publication year of all included studies), adjusted to smoking (Yes, No), and quality score (<8.5 vs. >8.5, based on the median quality score of all included studies). Eventually, we assessed publication bias using contour-enhanced funnel plots and Egger's tests [20, 21].

Nine studies reported dose-response information, four of which assessed cadmium from sources not directly comparable to internal measures or without the necessary numbers for calculation. Therefore, five studies [26, 23, 30, 31, 35] reporting internal cadmium levels (urine, blood, serum, plasma, or toenails) were included in a random-effects meta-regression using REML estimation with Knapp-Hartung adjustment to explore the association between increasing cadmium exposure and pancreatic cancer risk [22]. All analyses were performed using Stata software version 18.5 (StataCorp LLC, College Station, TX, USA).

3. Results

The literature search identified 2,000 studies from PubMed, EMBASE, and Scopus. After removal of duplicates, followed by title and abstract screening and full-text review, 18 studies (twenty records) met the inclusion criteria and were included in the qualitative synthesis and meta-analysis (Supplementary Figure 1) [23-40]. They consisted of ten cohort studies [24, 27, 31-34, 36-39], six case-control studies [23, 25, 26, 28, 30, 40], and two nested case-control studies [29, 35]. Six studies were conducted in North America [24, 26, 28, 31, 35, 40], seven in Europe [23, 29, 30, 32, 34, 38, 39], and five in Asia [25, 27, 33, 36, 37]. Cadmium exposure was assessed using occupational records in six studies

[26, 32, 34, 38-40], biological markers in 11 studies [23-26, 28-31, 35-37], dietary intake in one study [27], and environmental indicators in two studies [26, 33]. Pancreatic cancer incidence was evaluated in 11 studies [23, 25-30, 34, 35, 38, 40], while seven studies [24, 31-33, 36, 37, 39] assessed mortality. Most studies reported adjusted risk estimates, controlling for age, gender, body mass index (n=6) [24, 27, 29, 31, 35, 37], tobacco smoking (n=13) [23-29, 31, 33, 35, 37, 38, 40], and other relevant covariates (Table 1).

Figure 1 shows the forest plot of the association between cadmium exposure and pancreatic cancer risk by exposure source using random-effects models. Overall, 20 risk estimates from 18 studies were included in the meta-analysis, indicating a statistically significant increase in the risk of pancreatic cancer associated with cadmium exposure (RR = 1.69, 95% CI: 1.28-2.22), with substantial heterogeneity (I^2 = 96.4%, p < 0.001). Occupational cadmium exposure was evaluated in 6 studies and was associated with an increased risk

Table 1. Selected characteristics of studies on cadmium exposure and pancreatic cancer.

Ref.	Country	Study design	Gender	Source of Cd	Outcome	Risks (CI95%)	If adjusted (list of variables)
Amaral, 2012 [23]	Spain	Hospital-based case-control study	Both	Toenails	I	OR:2.09(1.37_3.17)	Age, Gender, Region, Smoking status, Education, Diabetes, Mutual adjustment for relevant trace elements
Adams, 2012 [24]	USA	Prospective population-based cohort study (NHANES III)	Both	Urinary	M	HR:1.27(0.88_1.83)	Age, smoking history, BMI, education, race
			Male			HR:3.95(1.94_8.04)	
			Female			HR:0.84(0.55_1.29)	
Kriegel, 2006 [25]	Egypt	Hospital-based case-control study	Both	Serum	I	OR:1.12(1.04_1.23)	age, gender, province (Dakahlia), and smoking
Luckett, 2012 [26]	USA	Population-based case-control study	Both	Occupational	I	OR:1.69(0.14_20.39)	smoking, education, alcohol, family history, age, gender, region
				Urinary		OR:5.14(3.001_8.819)	
				Well water		OR:1.51(0.77_2.97)	
Sawada, 2012 [27]	Japan	Prospective population-based cohort	Both	Food intake	I	HR:1.26(0.95_1.66)	Age, area, BMI, smoking status, frequency of alcohol intake, leisure-time physical activity, intake of meat, soybean, vegetable, fruit, menopausal status, use of exogenous female hormones.
			Male			HR:1.36(0.87_1.98)	
			Female			HR:1.13(0.72_1.72)	
Carriga, 2007 [28]	USA	Case control study	Both	Pancreatic juice Cd (μg/L)	I	OR:1.18(0.56_2.5)	Age, gender, and smoking history
Duell, 2018 [29]	European countries	Nested case-control study within a prospective cohort (EPIC)	Both	Blood	I	OR:1.13(1.01_1.27)	Age, Gender, Study center, Smoking, Alcohol intake, BMI, Diabetes, Education, Other metals (Zn, Se)
Djordjevic, 2019 [30]	Serbia	Hospital-based case-control study	Both	Tissue	I	OR:13.31(10.75_16.5)	age and gender
			Male			OR:12.25(0.29_17.06)	
			Female			OR:14.11(0.44_18.64)	
Garca-Esquinas, 2014 [31]	USA	Prospective cohort study (Strong Heart Study)	Both	Urinary	M	HR:2.4(1.39_4.17)	Gender, age, smoking status, cigarette pack-years, BMI

Ref.	Country	Study design	Gender	Source of Cd	Outcome	Risks (CI95%)	If adjusted (list of variables)
Järup, 1998 [32]	Sweden	Retrospective occupational cohort study	Both	Occupational (Battery workers)	M	SMR:1.58(0.77_3.22)	Age, and gender
			Male			SMR:1.48(0.54_3.23)	
			Female			SMR:2.2(0.55_12.3)	
Nishijo, 2018 [33]	Japan	Population-based prospective cohort study	Both	The Cd-polluted areas (environmental exposure)	M	SMR:0.85(0.52_1.39)	Age, smoking status, and hypertension
			Male			SMR:1.15(0.6_2.4)	
			Female			SMR:0.67(0.4_1.3)	
Nyqvist, 2017[34]	Sweden	Population cohort study	Both	Occupational (Glassworks Sites)	I	SIR:1.32(1.1_1.58)	Age, and gender
			Male			SIR:1.4(1.07_1.79)	
			Female			SIR:1.24(0.93_1.62)	
Stolzenberg-Solomon, 2025 [35]	USA	Nested case-control study within a prospective cohort (PLCO Trial)	Both	Blood	I	OR:1.25(1.09_1.43)	Age, gender, race, and smoking, BMI, diabetes, alcohol use, education, physical activity, family history, and dietary factors
Sakurai,2021 [36]	Japan	population-based cohort study	Both	Urinary	M	HR:0.94(0.57-1.55)	Age
			Male			HR:0.86(0.39-1.90)	
			Female			HR:1(0.53-1.89)	
Sorahan,1995 [39]	England	Retrospective occupational cohort study	Male	Occupational (copper cadmium alloy workers)	M	SMR:2.18(0.59_5.58)	Age, year of starting work, factory, time since starting work.
Watanabe, 2020 [37]	Japan	Prospective cohort study	Both	Urinary	M	RR:1.13(1.03_1.24)	smoking, alcohol consumption, age, BMI, blood pressure, hypertension, living area
Weiderpass, 2003 [38]	Finland	Population-based cohort study with job-exposure matrix (JEM)	Female	Occupational	I	RR:1.35(0.97_1.86)	birth cohort, calendar period, and socioeconomic status; smoking (pancreatic cancer)
Zhang, 2005 [40]	USA	Population-based case-control study	Male	Occupational (Chemicals and allied products)	I	OR:3.5(1.3_9.2)	Age, Smoking status and duration, Physical activity, Red meat intake, Fruit intake, Family history of pancreatic cancer

BMI: body mass index, I: Incidence, M: Mortality,

of pancreatic cancer (RR = 1.38, 95% CI: 1.19-1.61), with no evidence of heterogeneity (I^2 = 0.0%, p = 0.477).

Exposure assessed using serum or blood biomarkers was examined in 3 studies, yielding a modest but statistically significant association (RR = 1.15, 95% CI: 1.08-1.22), with no heterogeneity (I^2 = 0.0%, p = 0.384). Urinary cadmium exposure was assessed in 5 studies and was associated with an increased risk of pancreatic cancer (RR = 1.69, 95% CI: 1.04-2.75); however, substantial heterogeneity was observed within this subgroup (I^2 = 89.1%, p < 0.001).

A statistically borderline difference between exposure-source subgroups was observed (p for heterogeneity between groups = 0.047).

Contour-enhanced funnel plots are shown in Supplementary Figure 2. Egger's test provided limited evidence of publication bias overall, although some asymmetry was observed for studies using urinary cadmium measurements (P = 0.045). No

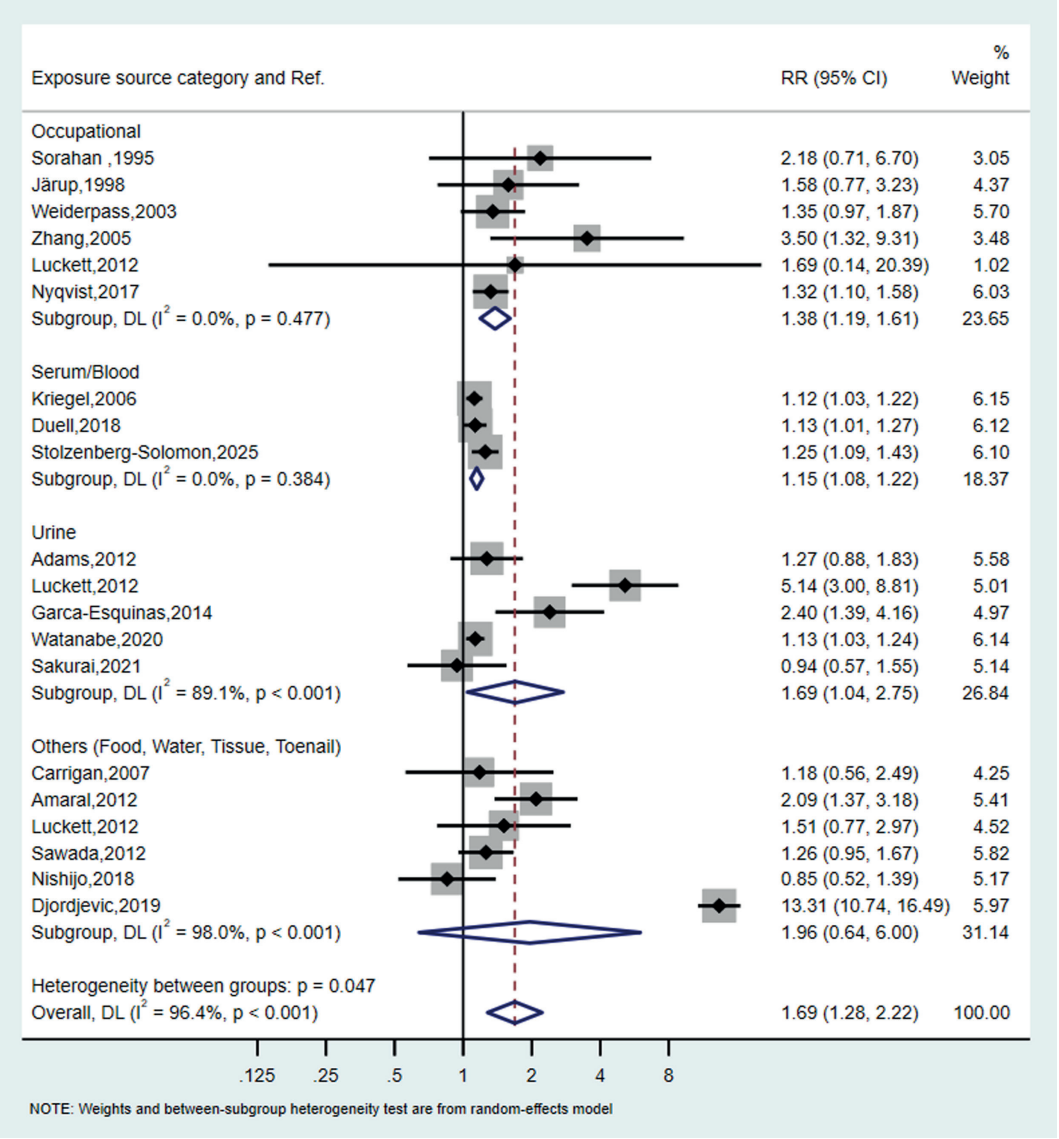

Figure 1. Forest plot (random-effects model) showing the association between cadmium exposure and pancreatic cancer by different exposure sources.

bias was detected for occupational, serum/blood, or other exposure sources.

Results of the stratified meta-analyses are presented in Table 2. By geographic region, a significant association was observed in North American studies (RR = 1.89, 95% CI: 1.28-2.81), and others (Japan and Egypt) (RR = 1.12, 95% CI: 1.06-1.19), whereas estimates from Europe were higher but imprecise (RR = 2.13, 95% CI: 0.95-4.75),with evidence of heterogeneity across regions (p_heterogeneity = 0.012). Stratification by gender showed an increased risk among men (RR = 1.71, 95% CI: 1.23-2.40) but not among women (RR = 1.13, 95% CI: 0.87-1.46); studies including both genders also showed an elevated risk (RR = 1.65, 95% CI: 1.22-2.22), with no heterogeneity between genders (p_heterogeneity = 0.073). Case-control studies reported higher risk estimates (RR = 2.20, 95% CI:

Table 2. Results of the meta-analysis of studies on overall association between cadmium exposure and pancreatic cancer stratified by Country, Year of publication, Quality score, Gender, Outcome, Study design, Smoking adjustment.

Characteristic	N Risk Estimates	RR, 95% CI	p Heterogeneity
Country			
North America (USA)	8	1.89 (1.28-2.81)	0.012
European Countries (Finland, England, Serbia, Spain, Sweden)	7	2.13 (0.95-4.75)	
Other Countries (Japan, Egypt)	5	1.12 (1.06-1.19)	
Year Of Publication			
<=2011	6	1.33 (1.05-1.70)	0.179
>2011	14	1.73 (1.29-2.33)	
Quality Score			
Low (< =8.5)	13	2.04 (1.39-3)	0.008
High (> 8.5)	7	1.19 (1.08-1.31)	
Gender			
Male	9	1.71 (1.23-2.40)	0.073
Female	8	1.13 (0.87-1.46)	
Both	17	1.65 (1.22-2.22)	
Outcome			
Incidence	13	1.92 (1.29-2.87)	0.060
Mortality	7	1.24 (0.99-1.55)	
Study Design			
Cohort	10	1.21 (1.07-1.37)	0.029
Case Control	10	2.20 (1.31-3.72)	
Smoking Adjustment			
No	5	2.26 (0.61-8.38)	0.445
Yes	15	1.36 (1.19-1.54)	

1.31-3.72) than cohort studies (RR = 1.21, 95% CI: 1.07-1.37), with evidence of heterogeneity (p_heterogeneity = 0.029). Studies published after 2011 showed stronger associations (RR = 1.73, 95% CI: 1.29-2.33) than those reported in earlier studies (RR = 1.33, 95% CI: 1.05-1.70). Associations were stronger for pancreatic cancer incidence (RR = 1.92, 95% CI: 1.29-2.87) than for mortality (RR = 1.24, 95% CI: 0.99-1.55), with no heterogeneity by either outcome or year-of-publication groups.

Further stratification by smoking adjustment indicated that studies that adjusted for smoking showed an RR = 1.36 (95% CI: 1.19-1.54), whereas studies that did not report a substantially higher RR = 2.26 (95% CI: 0.61-9.38) (p_heterogeneity = 0.445). Stratification by study quality revealed that studies with lower Newcastle-Ottawa Scale scores (<8.5) reported higher pooled estimates (RR = 2.04, 95% CI: 1.39-3.00) compared with high-quality studies (>8.5) (RR = 1.19, 95% CI: 1.08-1.31), with evidence of heterogeneity (p_heterogeneity = 0.008).

Table 3 summarizes the results of five studies [26, 23, 31, 35, 30] that evaluate pancreatic cancer risk across categories of cadmium exposure. A random-effects meta-regression including 14 estimates from five studies assessing internal cadmium measures was conducted to evaluate a linear dose-response

Table 3. Relative risk of pancreatic cancer by level of exposure to cadmium.

Ref.	Source of Cd	Dose Categories	Mid-Dose	Case	Control	Total	Estimates (CI 95%)
Luckett, 2012, USA [26]	Urine	<0.5 microgram/g creat.	0.25	10	71	81	OR: ref
		0.5<1 microgram/g creat.	0.75	16	33	49	OR:3.34(1.38-8.07)
		1<1.5 microgram/g creat.	1.25	13	18	31	OR:5.58 (2.03-15.34)
		>1.5 microgram/g creat.	1.75	24	19	43	OR:7.7(3.06-19.34)
Amaral, 2012, Spain [23]	Toenails	≤ 8.0 ng/g	5.35	17	100	117	OR: ref
		8.1-13.4 ng/g	10.75	11	99	110	OR:0.87 (0.37-2.03)
		13.5-29.1 ng/g	21.3	27	100	127	OR:2.04 (1-4.17)
		> 29.1 ng/g	36.9	59	99	158	OR:3.58 (1.86-6.88)
Garca-Esquinas, 2014, USA [31]	Urine	<0.70 microgram/g creat.	0.45	12	1257	1269	HR: ref
		0.71-1.22 microgram/g creat.	0.97	0	0	0	HR:0 (0-0)
		>1.23 microgram/g creat.	1.49	12	1245	1257	HR:2.47 (1.01-6.03)
Stolzenberg-Solomon, 2025, USA [35]	Blood	male= 0.27, female=0.31 µg/L	0.27	57	128	185	OR: ref
		male=0.34, female=0.38 µg/L	0.34	55	127	182	OR:1.06 (0.66-1.69)
		male=0.41, female=0.47 µg/L	0.83	49	127	176	OR:0.85 (0.52-1.38)
		male=0.52, female=0.59 µg/L	0.52	56	127	183	OR:1.04 (0.64-1.68)
		male=2.32, female= 3.13 µg/L	0.25	101	127	228	OR:1.81 (1.12-2.95)
Djordjevic, 2019, Serbia [30]	Tissue	<0.491 µg/g	0.46	6	10	16	OR: ref
		0.491-0.558 µg/g	0.52	1	4	5	OR:2.19 (0.67-7.1)
		0.558-0.966 µg/g	0.76	3	5	8	OR:3.2 (1.05-9.47)
		>0.966 µg/g	1.17	21	10	31	OR:3.99 (1.136-11.67)

Three studies (Nishijo et al., 2018, Japan; Sawada et al., 2012, Japan; and Weiderpass et al., 2003, Finlandreported dose-response relationships. However, they were not included in the dose-response analysis because they assessed different sources of exposure. Also, one study (Sakurai et al., 2021, Japan) was not included in the dose-response analysis because it did not report the necessary quantitative data required to perform the analysis.

relationship. The dose variable, expressed per 1 unit increase, was not statistically significant (RR = 1.28, 95% CI: 0.75-2.21; p = 0.334), indicating no evidence of a linear trend.

Substantial residual heterogeneity remained after adjustment (I^2 res = 72.2%), and the adjusted R^2 suggested that dose explained little of the between-study variability (Table 4).

4. Discussion

In this systematic review and meta-analysis of 18 observational studies, we found that cadmium exposure was associated with an increased risk of pancreatic cancer. Overall, individuals exposed to cadmium had a 69% higher risk of pancreatic cancer compared with those with no exposure. Elevated risks were consistently observed across different sources of exposure, with the strongest and most homogeneous associations seen in studies of occupational exposure, followed by studies using urine and then Blood/serum cadmium biomarkers. Stratified analyses revealed stronger associations in men than in women, and these associations were more pronounced in case-control studies compared with cohort studies. We observed evidence of publication bias in the studies related to urinary cadmium. Meta-regression analyses were based on limited data and did not reveal a clear linear dose-response relationship, and the substantial residual heterogeneity suggests that variations in exposure assessment and study characteristics may contribute to the observed differences.

Table 4. Random-effects meta-regression of dose on log odds ratio of cadmium exposure and risk of pancreatic cancer.

Variable	exp(β)	95% CI	p-value
Dose (per 1 unit)	1.28	0.75-2.21	0.334
Intercept	1.69	0.90-3.19	0.095

Model details: REML estimation; Knapp-Hartung modification; $\tau^2 = 0.353$; $I^2\_res = 72.2\%$; *adjusted* $R^2 = -4.7\%$; *n = 14 studies.*

Our findings are consistent with and extend previous evidence linking cadmium exposure to pancreatic cancer risk. Fanfani et al. (2024) provided a broad synthesis of cadmium-related cancer outcomes based on biological measures but did not conduct a pancreas-specific quantitative meta-analysis [41]. In contrast, our study focuses explicitly on pancreatic cancer, incorporates more recent studies, and provides pooled risk estimates with detailed stratification by exposure source and study characteristics. Our results align with the recent meta-analysis by Soleimani et al. (2025), which also reported a positive association between cadmium exposure and pancreatic cancer. Compared to that analysis, our study included additional recent evidence, distinguished between incidence and mortality outcomes, and explored heterogeneity by exposure circumstance, revealing stronger and more consistent associations in occupational and biomarker-based studies [42]. While Lee et al. (2025) reported evidence of a dose-response relationship, we did not observe a statistically significant linear trend, possibly due to differences in exposure harmonization, analytical approach, and the limited number of studies with comparable internal dose metrics[43]. Finally, our findings expand upon the earlier meta-analysis by Chen et al. (2015) by incorporating occupational exposures and more recent cohort and nested case-control studies, supporting the robustness of the association across diverse populations and exposure pathways [44].

Several biological mechanisms support the hypothesis of a causal link between cadmium exposure and the development of pancreatic cancer: (i) Cd is a strong inducer of oxidative stress, which leads to the production of reactive oxygen species. This can result in lipid peroxidation, protein oxidation, and oxidative damage to DNA [45-46]. (ii) Although Cd is not mutagenic, it disrupts multiple DNA repair pathways, including nucleotide excision repair and base excision repair. This interference enhances genomic instability and increases the risk of malignant transformation [47-48]. (iii) Additionally, Cd acts as an endocrine disruptor and tends to accumulate in the pancreas. Experimental studies have demonstrated that it causes toxicity to pancreatic β-cells, impairs insulin secretion, and disrupts glucose homeostasis. These mechanisms may link cadmium exposure to a higher risk of diabetes and pancreatic cancer [49]. (iv) Cd also promotes chronic inflammation by activating pro-inflammatory signaling pathways and altering immune responses, which creates a microenvironment conducive to tumor growth [50-51].

Considerable heterogeneity was observed across the available studies, with an overall I^2 of 96%, indicating substantial variability beyond chance. Stratified analyses by exposure source, study design, gender, and outcome type partially explained this heterogeneity. For instance, heterogeneity was reduced in studies examining occupational cadmium exposure and in blood/serum biomarker-based studies, suggesting that differences in exposure circumstances contributed to variability in effect estimates. The long biological half-life and bioaccumulation of cadmium may also contribute to between-study heterogeneity, as studies relying on occupational histories or biomarkers capture cumulative exposure more effectively than those based on short-term or indirect exposure assessments [52].

The association between cadmium exposure and outcomes was stronger in men than in women. This may be due to higher levels of occupational exposure among men, possible interactions with

smoking, or gender-specific biological susceptibility to cadmium-induced pancreatic toxicity [53]. Tobacco smoking is both an important source of cadmium exposure and an established risk factor for pancreatic cancer [54]. Smoking may therefore act as a confounder in studies examining cadmium and pancreatic cancer. Most studies included in our review adjusted for smoking, and associations remained significant, suggesting that cadmium exposure may contribute to pancreatic cancer independent of tobacco smoking. However, residual confounding cannot be entirely excluded, particularly in studies relying on self-reported smoking or biomarker-based exposure assessments.

In terms of study design, case-control studies generally reported higher effect estimates than cohort studies. This difference may be attributable to recall or selection biases commonly associated with retrospective designs. In contrast, cohort studies tended to yield more conservative and methodologically robust estimates; however, many did not fully adjust for potential confounders [55]. Geographic differences were also observed: studies conducted in North America typically reported stronger associations compared to those from Japan and Europe. This variation may be attributed to differences in cadmium exposure levels, dietary sources, occupational regulations, or genetic and lifestyle factors, as well as to the limited number of studies from other regions.

This study has several strengths. We conducted a thorough literature search across multiple databases (PubMed, EMBASE, and Scopus) following PRISMA guidelines. Our analysis focused specifically on pancreatic cancer and addressed the risk associated with multiple sources of cadmium exposure, including occupational exposure, biological markers, dietary intake, and environmental indicators. We also performed stratified and subgroup analyses based on exposure source, gender, study design, geographic region, and outcomes.

However, there are some limitations to note. Exposure misclassification is possible due to variability in cadmium assessment methods and reliance on single-biomarker measurements or occupational classifications. There was a limited number of studies from regions outside North America, and only a few studies were included in the dose-response analysis. Future research should focus on large, prospective studies using standardized cadmium biomarkers and gender-specific analyses to clarify exposure-risk relationships.

5. Conclusion

In conclusion, this study suggests a positive association between cadmium exposure and pancreatic cancer risk, particularly in occupational and biomarker-based studies. However, substantial heterogeneity, potential residual confounding, and limited dose response data needed cautious interpretation.

Supplementary Materials: The following are available online: Table S1a. PRISMA Checklist, Table S1b. PRISMA Abstract Checklist, Table S2. Detailed search strategy used on the different databases, Table S3. Modified version of the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies adopted for quality assessment, Table S4: Quality Assessment of Included Studies Using the Newcastle-Ottawa Scale (NOS) mentioned in supplementary table 3, Figure S1. Flowchart describing the study selection process, Figure S2. Funnel plot results in the association between cadmium exposure and pancreatic cancer by different exposure sources.

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References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74[3]:229-263. Doi: 10.3322 /caac.21834. Epub 2024 Apr 4. PMID: 38572751.

2. Arnold M, Abnet CC, Neale RE, et al. Global burden of 5 major types of gastrointestinal cancer. *Gastroenterology*. 2020;159:335-349.e15.
3. Walter FM, Mills K, Mendonça SC, et al. Symptoms and patient factors associated with diagnostic intervals for pancreatic cancer [SYMPTOM pancreatic study]: a prospective cohort study. *Lancet Gastroenterol Hepatol*. 2016;1[4]: 298-306. Doi: 10.1016/S2468-1253[16]30079-6.
4. Cai J, Chen H, Lu M, et al. Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis. *Cancer Lett.* 2021;520:1-11. Doi: 10.1016/j.canlet.2021.06.027. Epub 2021 Jun 30. PMID: 34216688.
5. Antwi SO, Eckert EC, Sabaque CV, et al. Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer. *Cancer Causes Control*. 2015;26[11]:1583-91. Doi: 10.1007/s10552-015-0652-y. Epub 2015 Aug 21. PMID: 26293241; PMCID: PMC4624268.
6. Johri N, Jacquillet G, Unwin R. Heavy metal poisoning: the effects of cadmium on the kidney. *Biometals*. 2010;23(5):783-92. Doi: 10.1007/s10534-010-9328-y. Epub 2010 Mar 31. PMID: 20354761.
7. Agency for Toxic Substances and Disease Registry [ATSDR]. Toxicological profile for cadmium. Atlanta [GA]: U.S. Department of Health and Human Services, Public Health Service; 2012.
8. International Agency for Research on Cancer. Cadmium and cadmium compounds. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 100C. Lyon, France: IARC; 2012.
9. Snoj Tratnik J, Kocman D, Horvat M, et al. Cadmium exposure in adults across Europe: Results from the HBM4EU Aligned Studies survey 2014-2020. *Int J Hyg Environ Health*. 2022;246:114050. Doi: 10.1016/j.ijheh.2022.114050. Epub 2022 Oct 17. PMID: 36265402.
10. Järup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure--a review of the literature and a risk estimate. *Scand J Work Environ Health*. 1998;24 Suppl 1:1-51. Erratum in: *Scand J Work Environ Health* 1998;24(3):240. PMID: 9569444.
11. European Food Safety Authority. Scientific opinion of the Panel on Contaminants in the Food Chain on a request from the European Commission on cadmium in food. *EFSA J*. 2009;980:1-139. Doi: 10.2903/j.efsa.2009.980.
12. World Health Organization. Cadmium in drinking water: background document for development of WHO Guidelines for Drinking water Quality. Geneva: World Health Organization; 2010. WHO/SDE/WSH/03.04/80. Available from: https://iris.who.int/handle/10665/75364
13. Thévenod F. Cadmium and cellular signaling cascades: to be or not to be? *Toxicol Appl Pharmacol.* 2009;238(3):221-39. Doi: 10.1016/j.taap.2009.01.013. Epub 2009 Jan 29. PMID: 19371614.
14. Filipič M. Mechanisms of cadmium induced genomic instability. *Mutat Res*. 2012;733(1-2):69-77. Doi: 10.1016/j.mrfmmm.2011.09.002. Epub 2011 Sep 17. PMID: 21945723.
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021. 372, n. 71. https://doi.org/10.1136/bmj.n71
16. Wells G A, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale [NOS] for assessing the quality of non-randomised studies in meta-analyses. Ottawa Hospital Research Institute. 2011. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
17. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*, 2010;36[3]:1-48. Doi: https://doi.org/10.18637/jss.v036.i03
18. Higgins J P T, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. Doi: https://doi.org/10.1136/bmj.327.7414.557
19. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*, 1998;280(19):1690-1691.
20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*, 1997;315(7109):629-634. Doi: https://doi.org/10.1136/bmj.315.7109.629
21. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol*, 2008:61(10):991-996. Doi: https://doi.org/10.1016/j.jclinepi.2007.11.010
22. van Aert RCM, Jackson D. A new justification of the Hartung-Knapp method for random-effects meta-analysis based on weighted least squares regression. *Res Synth Methods*. 2019;10(4):515-527. Doi: 10.1002/jrsm.1356. Epub 2019 Aug 14. PMID: 31111673; PMCID: PMC6973024.
23. Amaral AFS, Porta M, Silverman DT, et al. Pancreatic cancer risk and levels of trace elements. *Gut*. 2012;61(11): 1583-1588. Doi: 10.1136/gutjnl-2011-300264.
24. Adams SV, Passarelli MN, Newcomb PA. Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort. *Occup Environ Med*. 2012;69(2):153-156. Doi: 10.1136/oemed-2011-100111. Epub 2011 Nov 7. PMID: 22068173; PMCID: PMC3289533.
25. Kriegel AM, Soliman AS, Zhang Q, et al. Serum cadmium levels in pancreatic cancer patients from the East Nile Delta region of Egypt. *Environ Health Perspect*. 2006;114(1):113-119. Doi: 10.1289/ehp.8035. PMID: 16393667; PMCID: PMC1332665.
26. Luckett BG, Su LJ, Rood JC, Fontham ETH. Cadmium exposure and pancreatic cancer in South Louisiana. *J Environ Public Health*. 2012;2012:180186. Doi: 10.1155/2012/180186.
27. Sawada N, Iwasaki M, Inoue M, et al. Long-term dietary cadmium intake and cancer incidence.

Epidemiology. 2012;23(3):368-376. Doi: 10.1097/EDE.0b013e31824d063c.
28. Carrigan PE, Hentz JG, Gordon G, et al. Distinctive heavy metal composition of pancreatic juice in patients with pancreatic carcinoma. *Cancer Epidemiol Biomarkers Prev.* 2007;16(12):2656-2663. Doi: 10.1158/1055-9965.EPI-07-0332.
29. Duell E, Lujan-Barroso L, Outzen M, et al. Prediagnostic erythrocyte cadmium, selenium, and zinc levels and pancreatic cancer risk in Europe. *Pancreatology*. 2018;18(4 Suppl).
30. Djordjevic VR, Wallace DR, Schweitzer A, et al. Environmental cadmium exposure and pancreatic cancer: Evidence from case-control, animal and in vitro studies. *Environ Int.* 2019;128:353-361. Doi: 10.1016/j.envint.2019.04.048.
31. García-Esquinas E, Pollan M, Tellez-Plaza M, et al. Cadmium exposure and cancer mortality in a prospective cohort: the Strong Heart Study. *Environ Health Perspect.* 2014;122(4):363-370. Doi: 10.1289/ehp.1306587. Epub 2014 Feb 14. PMID: 24531129; PMCID: PMC3984227.
32. Järup L, Bellander T, Hogstedt C, Spång G. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. *Occup Environ Med.* 1998;55(11):755-759. Doi: 10.1136/oem.55.11.755. PMID: 9924452; PMCID: PMC1757526.
33. Nishijo M, Nakagawa H, Suwazono Y, et al. Cancer mortality in residents of the cadmium-polluted Jinzu River Basin in Toyama, Japan. *Toxics*. 2018 Apr 6;6(2):23. Doi: 10.3390/toxics6020023. PMID: 29642374; PMCID: PMC6027272.
34. Nyqvist F, Helmfrid I, Augustsson A, Wingren G. Increased cancer incidence in the local population around metal-contaminated glassworks sites. *J Occup Environ Med*. 2017;59(5). Doi: 10.1097/JOM.0000000000000984.
35. Stolzenberg-Solomon R, Jin D, Huang WY, Brockman J. Prediagnostic whole-blood cadmium and molybdenum associated with pancreatic cancer in an American cohort. *Am J Epidemiol.* 2025 7;194(5):1275-1284. Doi: 10.1093/aje/kwae165. PMID: 38965764; PMCID: PMC13070527.
36. Sakurai M, Suwazono Y, Nishijo M, et al. The relationship between the urinary cadmium concentration and cause-specific mortality in subjects without severe renal damage: a 35-year follow-up study in a cadmium-polluted area of Japan. *Int J Environ Res Public Health*. 2021;18(15):7747. Doi: 10.3390/ijerph18157747. PMID: 34360038; PMCID: PMC8345790.
37. Watanabe Y, Nogawa K, Nishijo M, et al. Relationship between cancer mortality and environmental cadmium exposure in the general Japanese population in cadmium non-polluted areas. *Int J Hyg Environ Health*. 2020;223(1):65-70. Doi: 10.1016/j.ijheh.2019.09.011.
38. Weiderpass E, Vainio H, Kauppinen T, Vasama-Neuvonen K, Partanen T, Pukkala E. Occupational exposures and gastrointestinal cancers among Finnish women. *J Occup Environ Med*. 2003;45(3):305-315. Doi: 10.1097/01.JOM.0000052963.43131.44.
39. Sorahan T, Lister A, Gilthorpe MS, Harrington JM. Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946-92. *Occup Environ Med.* 1995;52(12):804-812. Doi: 10.1136/oem.52.12.804. PMID: 8563843; PMCID: PMC1128381.
40. Zhang Y, Cantor KP, Lynch CF, Zhu Y, Zheng T. Occupation and risk of pancreatic cancer: a population-based case-control study in Iowa. *J Occup Environ Med*. 2005;47(4):392-398.
41. Fanfani A, Papini S, Bortolotti E, et al. Cadmium in biological samples and site-specific cancer risk and mortality: A systematic review of original articles and meta-analyses. *Cancer Epidemiol.* 2024;92:102550. Doi: 10.1016/j.canep.2024.102550. Epub 2024 Mar 12. PMID: 38480109.
42. Soleimani Y, Nayebi M, Mahmoudi S, et al. Cadmium exposure and risk of pancreatic cancer: Systematic review and meta-analysis. *PLoS One.* 2025;20(4):e0319283. Doi: 10.1371/journal.pone.0319283. PMID: 40299947; PMCID: PMC12040173.
43. Lee FJ, Inchai H, Lin JT, Koh D, Lin RT. Dose-response relationship of cadmium and pancreatic cancer risk: a meta-analysis. *Occup Environ Med.* 2025;82(8):407-414. Doi: 10.1136/oemed-2025-110163. PMID: 40962531; PMCID: PMC12573421.
44. Chen C, Xun P, Nishijo M, Sekikawa A, He K. Cadmium exposure and risk of pancreatic cancer: a meta-analysis of prospective cohort studies and case-control studies among individuals without occupational exposure history. *Environ Sci Pollut Res Int.* 2015;22(22):17465-74. Doi: 10.1007/s11356-015-5464-9. Epub 2015 Oct 1. PMID: 26423282; PMCID: PMC4654666.
45. Stohs SJ, Bagchi D, Hassoun E, Bagchi M. Oxidative mechanisms in the toxicity of chromium and cadmium ions. *J Environ Pathol Toxicol Oncol*. 2000;19(3):201-13. PMID: 10983887.
46. Thévenod F, Lee WK. Cadmium and cellular signaling cascades: interactions between cell death and survival pathways. *Arch Toxicol.* 2013;87:1743-1786. Doi: https://doi.org/10.1007/s00204-013-1110-9
47. Hartwig A. Mechanisms in cadmium-induced carcinogenicity: recent insights. *Biometals*. 2010;23(5):951-60. Doi: 10.1007/s10534-010-9330-4. PMID: 20390439.
48. Joseph P. Mechanisms of cadmium carcinogenesis. *Toxicol Appl Pharmacol.* 2009;238(3):272-9. Doi: 10.1016/j.taap.2009.01.011. Epub 2009 Feb 6. PMID: 19371617.
49. Joshua R. Edwards, Walter C. Prozialeck, Cadmium, diabetes and chronic kidney disease, *Toxicol Appl Pharmacol*. 2009;238(3):289-293. Doi: https://doi.org/10.1016/j.taap.2009.03.007.
50. Kolawole TA, Palacios J, Husaini DC, Nwokocha CR. Inflammation and Oxidative Stress Biomarkers in Heavy Metal Toxicity: Bridging the Gap to

Personalized Clinical Interventions. *J Appl Toxicol*. 2025;45(12):2546-2579. Doi: 10.1002/jat.4874. Epub 2025 Aug 14. PMID: 40813054.
51. Liu J, Qu W, Kadiiska MB. Role of oxidative stress in cadmium toxicity and carcinogenesis. *Toxicol Appl Pharmacol.* 2009;238(3):209-14. Doi: 10.1016/j.taap.2009.01.029. Epub 2009 Feb 21. PMID: 19236887; PMCID: PMC4287357.
52. Davidova S, Milushev V, Satchanska G. The Mechanisms of Cadmium Toxicity in Living Organisms. *Toxics.* 2024;12(12):875. Doi: 10.3390/toxics12120875. PMID: 39771090; PMCID: PMC11679562.
53. Lu H, Delnicki M, Griffin G, Wise JL. Current Understanding of Sex Differences in Metal-Induced Diseases. *Curr Environ Health Rep*. 2025;12(1):18. Doi: 10.1007/s40572-025-00482-x. PMID: 40202678; PMCID: PMC12168244.
54. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco Smoke and Involuntary Smoking. Lyon [FR]: International Agency for Research on Cancer; 2004. [IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 83.] Available from: https://www.ncbi.nlm.nih.gov/books/NBK316407/
55. Ahlbom A. Modern Epidemiology, 4th edition. TL Lash, TJ VanderWeele, S Haneuse, KJ Rothman. Wolters Kluwer, 2021. *Eur J Epidemiol.* 2021;36(8):767-768.Doi:10.1007/s10654-021-00778-w.Epub2021 Jul 3. PMID: 34216355; PMCID: PMC8416883.