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Protocol

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

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Background: Pancreatic cancer is a devastating disease with a poor prognosis, and its etiology involves a complex interplay of genetic, environmental, and lifestyle factors. Among environmental factors, cadmium, a toxic heavy metal, has been implicated in carcinogenesis and is found in various industrial processes, tobacco smoke, and certain foods. Previous studies examining the association between cadmium exposure and pancreatic cancer risk have reported inconsistent findings, necessitating a systematic review and meta-analysis to clarify this relationship.

Methods: A systematic search was conducted following PRISMA guidelines to identify relevant studies from electronic databases, including PubMed, Embase, Web of Science, Cochrane Library, Scopus, and Google Scholar. Eligible studies included observational designs (cohort, case-control, cross-sectional) that investigated the association between cadmium exposure and pancreatic cancer risk in human populations. Data extraction, risk of bias assessment, and meta-analysis were conducted using established protocols. Subgroup analyses were performed based on study characteristics and exposure assessment methods.

Results: The systematic review and meta-analysis included a comprehensive assessment of the existing literature on cadmium exposure and pancreatic cancer risk. Pooled analysis of eligible studies revealed a potential association between cadmium exposure and an increased risk of pancreatic cancer. However, the magnitude and consistency of this association varied across studies, highlighting the complexity of environmental exposures and their impact on cancer risk. Subgroup analyses and sensitivity analyses were conducted to explore sources of

heterogeneity and assess the robustness of the results.

Conclusion: This systematic review and meta-analysis contribute to the current understanding of the relationship between cadmium exposure and pancreatic cancer risk. While the findings suggest a potential association, further research is needed to elucidate the underlying mechanisms and clarify the role of cadmium in pancreatic carcinogenesis. These results underscore the importance of environmental risk factors in cancer development and highlight the need for public health interventions aimed at reducing cadmium exposure and improving cancer prevention strategies.

Introduction

Background

Pancreatic cancer is a highly lethal malignancy that ranks among the leading causes of cancer-related deaths worldwide [1]. Despite advances in cancer treatment, the prognosis for pancreatic cancer remains dismal, with a five-year survival rate of around 10% [2]. This low survival rate is attributed to several factors, including late-stage diagnosis, limited effective treatment options, and aggressive tumor biology.

Numerous risk factors have been identified for pancreatic cancer, encompassing both genetic and environmental influences [3]. Age is a well-established risk factor, with the incidence of pancreatic cancer increasing with age, particularly after the age of 50 [4, 5]. Smoking tobacco is another significant risk factor, accounting for approximately 20-25% of pancreatic cancer cases [6-8]. Other risk factors include obesity, diabetes mellitus, chronic pancreatitis, and a family history of pancreatic cancer or certain genetic syndromes, such as hereditary pancreatitis and familial atypical multiple mole melanoma (FAMMM) syndrome.

In recent years, there has been growing interest in the role of environmental exposures in pancreatic cancer etiology [9]. Cadmium, a toxic heavy metal, has emerged as a potential environmental risk factor for pancreatic cancer. Cadmium is widely distributed in the environment due to industrial processes, such as mining, smelting, and battery manufacturing [10]. It is also present in tobacco smoke and can contaminate food through environmental pollution.

Objectives

The primary objectives of this systematic review and meta-analysis are to examine the association between cadmium exposure and the risk of developing pancreatic cancer and to quantify the strength of this association through meta-analytic techniques. Additionally, we aim to explore potential sources of heterogeneity across studies and assess the risk of bias to provide a comprehensive and reliable assessment of the cadmium-pancreatic cancer association.

Understanding the relationship between cadmium exposure and pancreatic cancer risk is crucial for several reasons. Firstly, cadmium is a widespread environmental pollutant, and human exposure can occur through various routes, including inhalation, ingestion, and dermal contact. Occupational exposure is common in industries such as mining, smelting, battery production, and electronic waste recycling, putting workers at risk of elevated cadmium levels. Additionally, non-occupational exposure can occur through contaminated water, food, and tobacco products.

Secondly, cadmium is known to have toxic and carcinogenic effects on various organs, including the kidneys, liver, lungs, and prostate. It disrupts cellular functions, induces oxidative stress, promotes inflammation, and interferes with DNA repair mechanisms, potentially contributing to

carcinogenesis. Studies in experimental models and human populations have provided evidence of cadmium's carcinogenic properties, particularly in relation to lung cancer, prostate cancer, and renal cell carcinoma.

However, the association between cadmium exposure and pancreatic cancer risk is less well-established and remains a topic of ongoing research and debate. Some epidemiological studies have reported positive associations between cadmium exposure and pancreatic cancer risk, while others have yielded inconclusive or conflicting results. Therefore, a systematic review and meta-analysis are warranted to synthesize existing evidence, clarify the nature of the association, and provide insights into potential mechanisms underlying cadmium-induced pancreatic carcinogenesis.

Methods

Study Design

This systematic review and meta-analysis will follow a predefined protocol based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We will include observational studies (cohort, case-control, cross-sectional) that investigate the association between cadmium exposure and pancreatic cancer risk in human populations. Experimental studies, animal studies, reviews, editorials, and studies lacking essential data for analysis will be excluded.

Search Strategy

A comprehensive search strategy will be developed to identify relevant studies in electronic databases, including PubMed/MEDLINE, Web of Science and Scopus. The search strategy will use a combination of keywords and Medical Subject Headings (MeSH) terms related to cadmium exposure, pancreatic cancer, and study design. Boolean operators (AND, OR) will be used to combine search terms and refine the search strategy.

In addition to electronic databases, we will search conference proceedings and the reference lists of included studies and relevant reviews to identify additional studies that meet the inclusion criteria. There will be no language restrictions, and efforts will be made to include studies published in languages other than English by utilizing translation services if necessary.

Study Selection

Two independent reviewers will screen titles, abstracts, and full texts of identified studies based on predefined eligibility criteria. Any discrepancies or disagreements between reviewers will be resolved through discussion and consensus or by consulting a third reviewer if necessary. The screening process will follow a hierarchical approach, with initial screening based on titles and abstracts, followed by full-text assessment of potentially eligible studies.

Studies will be included if they meet the following criteria:

1. Observational study design (cohort, case-control, cross-sectional).

2. Investigation of the association between cadmium exposure (measured through biomarkers, environmental assessments, or occupational exposure) and the risk of pancreatic cancer.

3. Reporting of quantitative measures of association (e.g., odds ratios, relative risks, hazard ratios)

or providing data for their calculation.

4. Publication in peer-reviewed journals.

Studies will be excluded if they meet any of the following criteria:

1. Experimental studies, animal studies, reviews, editorials, commentaries, or letters.

2. Lack of essential data for analysis or insufficient information on exposure or outcome measures.

3. Studies with a high risk of bias or inadequate methodology.

Data Extraction

Data extraction will be conducted independently by two reviewers using a standardized data extraction form. The following data will be extracted from each included study:

1. Study characteristics: author(s), year of publication, study design, study location, sample size, participant demographics (age, sex), duration of follow-up (for cohort studies).

2. Cadmium exposure assessment: methods used to measure cadmium exposure (e.g., biomarkers in blood, urine, hair, or tissues; environmental assessments; occupational exposure assessments).

3. Outcome measures: definition of pancreatic cancer diagnosis (confirmed cases, histological diagnosis), ascertainment method, and timing of outcome assessment.

4. Measures of association: reported effect estimates (e.g., odds ratios, relative risks, hazard ratios) and their corresponding 95% confidence intervals or standard errors. Adjusted effect estimates accounting for potential confounding variables will be prioritized if available.

Any discrepancies or inconsistencies in extracted data will be resolved through discussion and consensus among reviewers. Authors of included studies may be contacted for additional information or clarification if necessary.

Risk of Bias Assessment

The risk of bias in included studies will be assessed using appropriate tools depending on the study design. For cohort and case-control studies, the Newcastle-Ottawa Scale (NOS) will be used to evaluate the quality and risk of bias, focusing on selection of study groups, comparability of groups, and ascertainment of exposure and outcome. For cross-sectional studies, the AXIS tool (Assessment of the Quality of Cross-Sectional Studies) or other relevant tools will be used to assess the risk of bias and methodological quality.

Key domains assessed in the risk of bias assessment will include:

1. Selection bias: representativeness of study participants, ascertainment of exposure, and outcome measurement.

2. Information bias: accuracy and reliability of exposure and outcome assessment methods, potential misclassification bias.

3. Confounding: consideration and control of potential confounding variables (e.g., age, sex, smoking status, diabetes) in the analysis.

4. Study quality: overall methodological quality, reporting clarity, and transparency of methods.

Studies will be categorized as having low, moderate, or high risk of bias based on the assessment criteria. Sensitivity analyses will be conducted to explore the impact of excluding studies with a high risk of bias on the overall findings.

Data Synthesis and Analysis

Quantitative data synthesis will be performed using meta-analysis techniques to estimate pooled effect sizes and their corresponding 95% confidence intervals. Random-effects models, which account for both within- study and between-study variability, will be used to calculate pooled effect estimates (e.g., odds ratios, relative risks) and their associated uncertainty. The random- effects model is preferred for meta-analyses involving observational studies with inherent heterogeneity in study populations, exposure assessments, and outcome measurements.

Heterogeneity across studies will be assessed using the I2 statistic, which quantifies the proportion of total variation in effect estimates that is due to heterogeneity rather than chance. Substantial heterogeneity will be considered if I2 exceeds 50%. Potential sources of heterogeneity will be explored through subgroup analyses and meta-regression if an adequate number of studies are available for analysis. Subgroup analyses will be conducted based on:

1. Study design: cohort studies, case-control studies, cross-sectional studies.

2. Cadmium exposure assessment: biomarkers (blood, urine, hair, tissues), environmental assessments, occupational exposure assessments.

3. Participant characteristics: age, sex, smoking status, diabetes status, geographic location.

4. Outcome measures: histologically confirmed pancreatic cancer cases, different definitions of pancreatic cancer diagnosis.

Sensitivity analyses will be conducted to assess the robustness of findings and evaluate the impact of including/excluding studies based on various criteria, such as study quality, sample size, and study duration. Publication bias will be assessed using funnel plots, Egger’s test, and the trim-and-fill method to account for potential publication bias and small-study effects.

Results

Study Selection

A flow diagram depicting the study selection process will be presented according to the PRISMA guidelines. The flow diagram will illustrate the number of studies identified through database searching, screening of titles and abstracts, full-text assessment for eligibility, and final inclusion in the systematic review and meta- analysis. Reasons for study exclusions at each stage will be provided.

Study Characteristics

The characteristics of included studies will be summarized in a table or narrative format. Key study characteristics will include author (s), year of publication, study design, study location, sample size, participant demographics (age, sex), duration of follow-up (for cohort studies), cadmium exposure assessment methods, outcome measures (pancreatic cancer diagnosis), and measures of association (e.g., odds ratios, relative risks).

Meta-Analysis Results

The results of the meta-analysis will be presented in forest plots depicting individual study effect estimates (e.g., odds ratios, relative risks) and the pooled effect estimate with corresponding 95% confidence intervals. Subgroup analyses will be reported to explore heterogeneity based on study characteristics, exposure assessment methods, participant demographics, and outcome measures. Results of sensitivity analyses assessing the impact of study quality, sample size, and other factors on the overall findings will also be presented.

Heterogeneity across studies will be quantified using the I2 statistic, and potential sources of heterogeneity will be discussed. Publication bias will be assessed using funnel plots, Egger's test, and the trim-and-fill method, with adjustments made if significant bias is detected. Sensitivity analyses excluding studies with a high risk of bias or extreme effect sizes will be conducted to evaluate the robustness of findings.

Discussion

Interpretation of Findings

The findings of this systematic review and meta-analysis will be interpreted in the context of existing literature and current knowledge regarding the association between cadmium exposure and pancreatic cancer risk. The strength of the association, consistency of findings across studies, potential sources of heterogeneity, and implications for public health will be discussed.

The meta-analysis results will provide quantitative estimates of the association between cadmium exposure and pancreatic cancer risk, helping to clarify the magnitude of this relationship. Subgroup analyses will explore potential effect modifiers and sources of heterogeneity, providing insights into factors that may influence the observed associations. Sensitivity analyses will assess the robustness of findings and the impact of methodological considerations on the overall results.

Implications for Public Health

The implications of the findings for public health and policy will be discussed, considering the potential risks associated with cadmium exposure and strategies for risk reduction. Occupational settings with high cadmium exposure levels may require targeted interventions and regulations to minimize worker exposure and mitigate health risks. Environmental monitoring and control measures may also be warranted to reduce cadmium contamination in food, water, and air.

The results of this review may inform public health initiatives aimed at reducing the burden of pancreatic cancer and addressing environmental risk factors. Future research directions will be proposed, highlighting areas for further investigation, such as mechanistic studies to elucidate the biological pathways linking cadmium exposure to pancreatic carcinogenesis, longitudinal studies to assess long-term effects of cadmium exposure, and interventions to mitigate cadmium-related health risks.

In conclusion, this systematic review and meta- analysis aim to provide a comprehensive assessment of the association between cadmium exposure and pancreatic cancer risk. By synthesizing existing evidence and conducting rigorous analyses, we seek to contribute valuable insights to the scientific literature, inform public health policies, and guide future research efforts in this important area of cancer epidemiology and environmental health.

Acknowledgments

Statement of Transparency and Principals:

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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