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The Impact of Artificial Sweetener Consumption on Cancer Risk: A Systematic Review of Epidemiological Evidence

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ADMINISTRATIVE INFORMATION

Support - Academic budget.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 August 2025 and was last updated on 12 August 2025.

INTRODUCTION

Review question / Objective In adults, does the consumption of artificial sweeteners compared to no consumption affect the risk of developing cancer?

Rationale Artificial sweeteners are widely used sugar substitutes promoted for weight control and glycemic regulation. Despite regulatory approval and widespread consumption, concerns remain about their potential carcinogenic effects. Existing epidemiological studies yield inconsistent findings due to methodological variability, such as differences in exposure assessments, populations, and outcome definitions. This systematic review aims to synthesize evidence from cohort studies to provide clearer insights into whether artificial sweetener consumption increases cancer risk. It employs a rigorous methodology aligned with PRISMA2020 and incorporates advanced statistical techniques for heterogeneity and bias management. Its findings will support evidence-based dietary recommendations, regulatory decisions, and future research directions.

Condition being studied The condition of interest is cancer—both overall incidence and site-specific cancers (e.g., colorectal, breast, lung). Cancer remains a major public health burden globally, and identifying modifiable dietary risk factors, such as artificial sweeteners, is critical for prevention strategies and policy-making.

METHODS

Search strategy A single pilot search will be conducted in the PubMed database (coverage: 1946–2024). Search terms were based on MeSH terms and Title/Abstract keywords:
– "Sweetening Agents"[Mesh] AND cancer[Title/Abstract]
– "Artificially Sweetened Beverages"[Mesh] AND cancer[Title/Abstract]
– "Non-Nutritive Sweeteners"[Mesh] AND cancer[Title/Abstract]
– "Aspartame"[Mesh], "Saccharin"[Mesh], "Cyclamates"[Mesh], "Stevia"[Mesh] AND cancer[Title/Abstract]

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No filters or language restrictions will be applied. A second and final search will be conducted solely in the PubMed database (coverage: 1946-2025) using the following search string: ((("Cohort Studies"[MeSH Terms] AND (("Sweetening Agents"[MeSH Terms] AND "cancer"[Title/Abstract]) OR ("Artificially Sweetened Beverages"[MeSH Terms] AND "cancer"[Title/Abstract]) OR (“Non-Nutritive Sweeteners"[MeSH Terms] AND "cancer"[Title/Abstract]) OR ("Stevia"[MeSH Terms] AND "cancer"[Title/Abstract]) OR ("Saccharin"[MeSH Terms] AND "cancer"[Title/Abstract]) OR (“Cyclamates"[MeSH Terms] AND "cancer"[Title/Abstract]) OR ("Aspartame"[MeSH Terms] AND "cancer"[Title/Abstract])))) NOT ("Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "Randomized Controlled Trial"[Publication Type])) AND ("loattrfree full text"[Filter] AND 1946/01/01:2025/12/31[Date – Publication])) AND ((ffrft[Filter]) AND (1946:2025[pdat])) No filters or language restrictions will be applied.

Participant or population Adults (≥18 years) from the general population with or without pre-existing metabolic conditions such as obesity or diabetes. Participants must be cancer-free at baseline.

Intervention Consumption of artificial sweeteners (e.g., aspartame, sucralose, acesulfame potassium, saccharin) through diet, beverages, or supplements. Exposure includes self-reported intake or biomarker assessments.

Comparator Participants with no artificial sweetener exposure, those consuming natural sweeteners (e.g., stevia), placebo, or no sweeteners.

Study designs to be included Study designs that can capture both causal inference and associative evidence across different levels of rigor. Cohort studies, Case–control studies, Nested case–control studies, RCTs with cancer outcomes.

Eligibility criteria
– Adults (≥18 years)
– Exposure to artificial sweeteners
– Comparator group without artificial sweetener use
– Cohort design
Exclusion:
– Children or cancer patients at baseline
– Animal/in vitro studies
– Case-control, RCTs, ecological studies, reviews
– Studies focusing solely on natural sweeteners
– Studies with poorly defined control groups.

Information sources The primary source is PubMed. No additional databases, grey literature, or author contacts will be used in this review.
Duplicate records will be identified and removed using Zotero. Title/abstract and full-text screening will be conducted independently by at least two reviewers, with discrepancies resolved through discussion or by a third reviewer.

Main outcome(s)
Overall cancer incidence
– Site-specific cancer incidence (e.g., breast, colorectal)
– Effect measures include risk ratios (RR), hazard ratios (HR), and odds ratios (OR) with 95% confidence intervals. Where multiple time points or models exist, the most fully adjusted model will be used.

Additional outcome(s)
– Subgroup-specific risks (e.g., by sweetener type, cancer type)
– Confounder adjustment strategies
– Method of exposure and outcome assessment.

Data management All search results retrieved from the selected electronic databases will be exported in a standardized bibliographic format (RIS or BibTeX) and imported into Zotero (version 7.0). Zotero will be used for the initial management of references, including storage, organization, and duplicate removal. Duplicate detection will be performed using Zotero’s “Duplicate Items” function, which identifies records with matching metadata (e.g., title, author, publication year, DOI). Where minor discrepancies in metadata exist, manual verification will be undertaken to ensure accurate deduplication without accidental record loss.
Following deduplication, the cleaned dataset will be exported from Zotero in RIS format and uploaded into a screening platform (e.g., Rayyan). Screening will be conducted in two sequential phases: (1) title and abstract screening, and (2) full-text review. Rounds of two reviewers will independently assess each record against the pre-defined inclusion and exclusion criteria. Discrepancies at either stage will be resolved through discussion; if consensus cannot be reached, a third reviewer will adjudicate.
During the screening process, the platform will be used to record decisions (include/exclude) and, for excluded studies, document the primary reason for exclusion. These reasons will be used to populate the PRISMA flow diagram and enhance transparency of the selection process.

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Full-text articles will be retrieved in PDF format, labeled systematically, and stored in a shared, access-controlled cloud repository to ensure secure access by all team members. Each included study will be assigned a unique identifier for cross-referencing between screening, data extraction, and analysis stages.
Data extraction will be performed using a pre-piloted electronic form developed in Microsoft Excel or Google Sheets. The extraction form will include fields for study characteristics (authors, year, country, design), participant details, intervention/exposure, comparator, outcomes, effect estimates, measures of variability, and funding/conflict of interest statements. Two reviewers will independently extract data from each included study, with discrepancies resolved through discussion or third-party adjudication.
Quality assessment of included studies will also be conducted in duplicate, using validated tools appropriate for each study design. Scores and judgments from the risk-of-bias assessment will be recorded in the same centralized data file.
All versions of the dataset, including raw search results, deduplicated records, screened records, and extracted data, will be archived in read-only format to preserve an audit trail. Data security will be maintained through password protection, regular backups, and restricted access to authorized team members only.

Quality assessment / Risk of bias analysis The ROBINS-I Version 2 tool is used to assess risk of bias in non-randomized studies across seven domains. Three reviewers assess independently; disagreements are resolved via discussion or adjudication. Judgments will inform sensitivity and GRADE certainty assessments.

Strategy of data synthesis A random-effects meta-analysis will be conducted using the DerSimonian–Laird estimator with Knapp–Hartung adjustment. Statistical heterogeneity will be assessed using the I^2 statistic and 95% prediction intervals. Forest plots, subgroup analyses, GOSH plots, and sensitivity analyses will be performed to explore heterogeneity and robustness of findings. If meta-analysis is not feasible, results will be synthesized narratively.

Subgroup analysis Subgroup analyses will be performed, where data permit, to explore potential sources of heterogeneity and assess whether the association between sweetener consumption and cancer risk varies across predefined characteristics. Planned subgroups include:
-Study design (prospective cohort, case–control, cross-sectional)
– Type of sweetener (e.g., aspartame, sucralose, saccharin, stevia)
– Level of exposure (low vs. high intake, as defined by each study)
– Cancer type (e.g., colorectal, breast, pancreatic)
– Sex (male, female)
– Geographical region (e.g., North America, Europe, Asia).

Sensitivity analysis Exclusion of high risk-of-bias studies: re-running meta-analyses after removing studies judged at high or critical risk of bias. Influence (leave-one-out) analysis: sequentially omitting each study to assess its impact on the pooled effect. Small-study effects: excluding small studies (e.g., n below study-specific threshold) to assess influence of imprecise estimates. Adjusted vs unadjusted estimates: comparing results using only multivariable-adjusted effect estimates versus crude estimates. Exclusion of industry-funded studies: where funding/conflict of interest is reported. Alternative meta-analytic models/estimators: repeating analyses with different τ^2 estimators (e.g., REML) and without Knapp–Hartung to check estimator sensitivity. Outcome/exposure definition sensitivity: restricting analyses to studies using comparable exposure metrics (e.g., grams/day or servings) or to prespecified cancer endpoints. Publication-bias adjustments: applying trim-and-fill and comparing with original pooled estimates when funnel asymmetry is suspected. Results of sensitivity analyses will be reported alongside primary results (tables and forest plots) and discussed in terms of consistency and implications for confidence in the findings.

Language restriction English, spanish.

Country(ies) involved Mexico.

Keywords Sweeteners; artificial sweeteners; aspartame; cancer.

Dissemination plans The findings of this review will be submitted for publication in a peer-reviewed journal and presented at relevant national and international scientific conferences. A plain-language summary will be prepared to share with public health stakeholders and made available through institutional or open-access repositories to maximize reach and accessibility.

Contributions of each author
Author 1 - Carlos Maximiliano Ramos-Medina - Methodology Lead • Contributed to refining eligibility criteria and the methodological approach for screening, data extraction, and quality assessment. • Will design and oversee the risk-of-

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bias assessment process. • Will contribute to drafting and reviewing the methods section. • Will coordinate author activities, and and resolve methodological queries.
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Author 2 - Andrea Carolina Valdes-Fernandez - Information Specialist / Literature Search • Will design and implement search strategies across multiple databases. • Will manage reference records, remove duplicates, and ensure search reproducibility documentation.
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Author 3 - Regina Villagomez-Gomez -Screening & Study Selection • Will conduct title/abstract screening and full-text assessment in duplicate. • Will maintain screening logs and contribute to the PRISMA flow diagram.
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Author 4 - Rodrigo Villanueva-Muzzi - Information Specialist / Literature Search • Will design and implement search strategies across multiple databases. • Will manage reference records, remove duplicates, and ensure search reproducibility documentation.
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Author 5 - Abimael Alcocer-Mena -Data Extraction & Quality Appraisal • Will extract epidemiological data and study characteristics.• Will perform risk-of-bias assessments independently. • Will assist in preparing descriptive summary tables.
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Author 6 - Fernanda Monserrath Ramirez-Toscano - Statistical Analysis • Will conduct meta-analyses using a random-effects model when applicable. • Will generate statistical outputs, including forest plots, funnel plots, and heterogeneity statistics. • Will interpret results for inclusion in the discussion.
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Author 7 - Fernando Antonio Ferreyro-Bravo - Nutritionist / Subject Matter Expert • Will provide expertise on dietary exposure measurement and nutritional epidemiology. • Will interpret findings in the context of diet, public health, and cancer prevention strategies. • Will critically revise the manuscript for accuracy and scientific relevance.
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Author 8 - Elda Leonor Pacheco Pantoja - Conceived and designed the review, formulated the research question and PICO framework. • Developed the review protocol and registered it with INPLASY. • Will supervise all phases of the project, coordinate author activities, and resolve methodological queries. • Will verify the accuracy and integrity of the data and analyses. • Will lead the drafting of the manuscript and integrate feedback from all authors. • Will act as the guarantor of the work.

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