DOI:10.31557/APJEC.2024.7.1.129

REVIEW

Aspartame Consumption and Cancer Risk: A Systematic Review and Meta-Analysis Protocol

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Abstract

Background: Aspartame, a widely used artificial sweetener, has been under scrutiny for its potential carcinogenic effects. Although early studies raised concerns about its link to cancer, particularly in animal models, more recent human studies have produced mixed results. This protocol aims to systematically review the association between aspartame consumption and cancer risk. **Methods:** A systematic review and meta-analysis will be conducted by searching databases including MEDLINE, Scopus, and Web of Science. Eligible studies will involve human participants exposed to aspartame and assess cancer incidence as the primary outcome. Data extraction will include study characteristics, exposure levels, and cancer outcomes. Risk of bias will be assessed using the Newcastle-Ottawa Scale, and data will be synthesized through qualitative and quantitative methods, including meta-analysis where applicable. **Results:** This review will present pooled risk estimates for cancer associated with aspartame consumption and explore variations by cancer type, dose, and duration of exposure. **Conclusion:** This study will provide an updated synthesis of evidence regarding aspartame consumption and its potential role in cancer development, informing future public health guidelines.

Keywords: Cancer- Aspartame- Protocol

Asian Pac Environ Cancer, **7 (1)**, 129-132

Submission Date: 10/10/2024 Acceptance Date: 11/04/2024

Introduction

Aspartame, one of the most widely used artificial sweeteners globally, has been the subject of scientific scrutiny regarding its potential link to cancer [1]. Early studies in the 2000s suggested that aspartame might increase the risk of certain cancers, particularly leukemia and lymphoma, based on findings in lab rats. However, these studies faced criticism due to methodological limitations, such as high doses of aspartame that do not reflect typical human consumption [2]. More recent epidemiological studies in humans have yielded mixed results. Some research, including large cohort studies like the NutriNet-Santé study, reported a modest increase in cancer risk, particularly for breast and obesity-related cancers, in people who consumed higher levels of aspartame. For instance, the NutriNet-Santé study found that individuals who consumed artificial sweeteners, especially aspartame, had a slightly elevated risk of overall cancer and specific cancers like breast cancer [3].

In 2023, the International Agency for Research on Cancer (IARC), part of the World Health Organization (WHO), classified aspartame as "possibly carcinogenic to humans" (Group 2B), based on limited evidence of a link to liver cancer. This classification reflects caution rather than certainty, indicating that while there is some evidence of carcinogenicity, it is not strong or conclusive. Alongside the IARC, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) conducted a separate evaluation and concluded that the current levels

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of aspartame consumption do not pose a significant cancer risk to the general population [4].

This ongoing debate underscores the complexity of evaluating aspartame's safety. While some epidemiological data suggest a modest increase in cancer risk with high aspartame consumption, other studies fail to confirm this association. The variation in study outcomes could be attributed to differences in study design, population characteristics, and the quantities of aspartame consumed. Given the uncertainty, health organizations like the American Cancer Society advocate for more high-quality research to clarify the potential cancer risks associated with aspartame and other artificial sweeteners [5].

While aspartame has been flagged as a possible carcinogen, particularly for liver cancer, the overall evidence remains mixed, and no regulatory body has yet deemed it a significant health hazard at current consumption levels. Ongoing research is crucial to fully understanding its safety profile.

Various observational studies and experimental research have produced conflicting results on this association, necessitating a systematic review and meta-analysis to assess the overall body of evidence. This protocol outlines the steps to conduct a systematic review to synthesize evidence on whether aspartame consumption is linked to an increased risk of cancer.

1.2. Objectives

The primary objective of this systematic review and meta-analysis is to:

• Assess the association between aspartame consumption and the risk of developing cancer.

• Explore whether the type of cancer, dosage, and duration of aspartame exposure affect this association.

1.3. Research Question

Is aspartame consumption associated with an increased risk of cancer in humans?

2. Methods

2.1. Eligibility Criteria

2.1.1. Types of Studies

We will include the following study designs:

• Observational studies (cohort, case-control, cross-sectional)

• Reviews or meta-analyses will be excluded, but their reference lists will be checked for eligible studies.

2.1.2. Participants

• Inclusion: Studies involving human participants of all ages and both genders, exposed to aspartame through diet.

• Exclusion: Studies on animals, in vitro studies, and participants with pre-existing cancer diagnoses before aspartame exposure.

2.1.3. Intervention/Exposure

• Exposure: Aspartame consumption, either quantified (e.g., in mg/kg/day) or categorized (e.g., low, medium, high intake).

2.1.4. Comparison

• Studies comparing participants exposed to aspartame with those not exposed or exposed to other sweeteners (saccharin, sucralose, etc.) will be included.

2.1.5. Outcomes

The primary outcome is cancer incidence, including any cancer type (e.g., colorectal, breast, prostate). Secondary outcomes may include cancer mortality and the development of pre-cancerous lesions.

2.1.6. Setting

There are no restrictions on study location or setting.

2.2. Information Sources

2.2.1. Databases

We will search the following electronic databases:

• MEDLINE (via PubMed)

• Scopus

• Web of Science

2.2.2. Other Sources

Reference lists of included studies and previous reviews will be hand-searched to identify additional eligible studies.

2.3 Search Strategy

The search strategy will be developed in consultation with a research librarian to ensure comprehensiveness. The strategy will use a combination of Medical Subject Headings (MeSH) terms and free text related to aspartame, cancer, and epidemiological study designs. Below is a draft search strategy for PubMed:

1. ("aspartame"[MeSH Terms] OR aspartame [Text Word])

2. ("neoplasms"[MeSH Terms] OR "cancer"[Text Word] OR "carcinogenesis"[Text Word])

3. ("cohort studies"[MeSH Terms] OR "case-control studies"[MeSH Terms] OR "cross-sectional studies"[MeSH Terms]

4. #1 AND #2 AND #3

This strategy will be adapted for other databases.

2.4. Data Management

2.4.1. Data Extraction and Management

All citations identified from the databases will be imported into EndNote (or another reference management software), and duplicates will be removed. Screening will be conducted using Covidence or Rayyan, a software designed for systematic reviews. A data extraction form will be developed in Microsoft Excel to collect relevant data from the studies, including:

• Study characteristics (author, year, location, design)

• Participant characteristics (sample size, demographics)

• Exposure details (dosage, duration, method of aspartame consumption)

• Outcome measures (cancer type, cancer incidence, follow-up duration)

• Risk estimates (odds ratios, relative risk, hazard ratios, and their 95% confidence intervals).

2.5. Selection Process

Two reviewers will independently screen titles and abstracts of retrieved records. Studies that meet the inclusion criteria will be subjected to full-text screening. Any disagreements between the reviewers will be resolved through discussion, and if necessary, a third reviewer will be consulted. A PRISMA flow diagram will be used to illustrate the study selection process.

2.6. Data Items

We will extract the following data from each included study:

• Study characteristics: First author, year of publication, study location, and design.

• Population: Number of participants, age, sex distribution, and health status.

• Exposure: Aspartame intake details, dosage levels, exposure duration.

• Outcome: Cancer type, incidence, mortality.

• Confounders: Adjustments made for possible confounders (e.g., smoking, diet, physical activity).

3. Results

3.1. Outcomes and Prioritization

The primary outcome is the risk of cancer incidence among individuals who consume aspartame compared to those who do not. We will also prioritize cancer type-specific risks where data is available, such as the risk of colorectal, breast, or prostate cancer.

Secondary outcomes include cancer mortality and pre-cancerous conditions, as well as the dose-response relationship between aspartame consumption and cancer risk.

3.2. Risk of Bias Assessment

The risk of bias will be assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS).

The NOS will evaluate studies on three main domains: selection of study groups, comparability of groups, and ascertainment of outcome. Each study will be classified as low, medium, or high risk of bias based on predefined criteria.

3.3. Data Synthesis

3.3.1 Qualitative Synthesis

We will first present a qualitative summary of included studies, grouped by study design (e.g., cohort, case-control) and by type of cancer. This narrative synthesis will highlight any trends in the association between aspartame consumption and cancer risk.

3.3.2 Quantitative Synthesis

Where feasible, we will pool data using a random-effects meta-analysis. A fixed-effects model may be used if there is little heterogeneity. Meta-analysis will be conducted using Stata. We will calculate pooled odds ratios (OR), relative risks (RR), or hazard ratios (HR), along with 95% confidence intervals (CIs), for cancer risk associated with aspartame consumption. We will include subgroup analyses based on:

• Type of cancer

• Gender

• Age group

• Dose of aspartame consumption

• Duration of exposure

3.4. Assessment of Heterogeneity

Heterogeneity across studies will be assessed using the I^2 statistic. I^2 values of 25%, 50%, and 75% will be considered low, moderate, and high heterogeneity, respectively. We will explore sources of heterogeneity using subgroup analysis and meta-regression.

3.5. Sensitivity Analysis

Sensitivity analyses will be conducted by:

• Excluding studies with a high risk of bias.

• Assessing the influence of each study by conducting a leave-one-out analysis (i.e., omitting one study at a time).

3.6. Publication Bias

We will assess publication bias using funnel plots and Egger's test for asymmetry. A symmetrical funnel plot will suggest a low risk of publication bias, while an asymmetrical plot will indicate potential bias.

4. Discussion

4.1 Grading the Quality of Evidence

The quality of evidence will be evaluated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. We will assess the certainty of the evidence based on the following domains:

• Risk of bias

• Consistency of results

• Directness of evidence

• Precision

• Publication bias

The overall quality of evidence for each outcome will be rated as high, moderate, low, or very low.

4.2. Ethical Considerations

No ethical approval is required for this systematic review and meta-analysis, as it does not involve collecting new data from human participants.

4.3. Dissemination

The results of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal and presented at relevant scientific conferences. We will also consider disseminating findings through open-access platforms to maximize accessibility.

References

1. Soffritti M. Understanding the link between aspartame and cancer. Expert Review of Anticancer Therapy. 2024 09;24(9):793-802. https://doi.org/10.1080/14737140.2024.2383675
2. Landrigan PJ, Straif K. Aspartame and cancer - new evidence for causation. Environmental Health: A Global Access Science Source. 2021 04 12;20(1):42. https://doi.org/10.1186/s12940-021-00725-y
3. Debras C, Chazelas E, Srour B, Druesne-Pecollo N, Esseddik Y, Szabo de Edelenyi F, Agaësse C, et al. Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study. PLoS medicine. 2022 03;19(3):e1003950. https://doi.org/10.1371/journal.pmed.1003950
4. (IARC) IAfRoC. Aspartame hazard and risk assessment results released 2023 [Available from: https://www.who.int/news/item/14-07-2023-aspartame-hazard-and-risk-assessment-results-released#:~:text=IARC%20classified%20aspartame%20as%20possibly%20carcinogenic%20to%20humans%20(Group%202B,a%20type%20of%20liver%20cancer).
5. (NCI) NCI. Artificial Sweeteners and Cancer 2023 [Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/artificial-sweeteners-fact-sheet.