The Bitter Truth Behind Artificial Sweeteners and Cancer Risk

Ayana Rao

Abstract

As obesity rates continue to rise around the world, many turn to low-sugar or sugar-free alternatives to avoid health complications. Diet and sugar-free foods and beverages utilize artificial sweeteners to achieve similar tastes while lacking the calories that table sugar has. However, concerns have been raised regarding the potential role artificial sweeteners may play in causing cancer, with numerous artificial sweeteners having preliminary data that suggests associations with cancers. In this review, we present the latest evidence for cancer-associated risk amongst US-approved artificial sweeteners and identify gaps for future research.

Introduction

The global rise in obesity has prompted the widespread adoption of low-calorie, non-nutritive sweeteners, also known as artificial sweeteners, in the food and beverage industry. These substitutes offer the appeal of sweetness without the added calories of sugar, making them attractive for weight management and mitigating health risks associated with excessive sugar intake. Approved artificial sweeteners vary by country; in the United States (US), the Federal Drug Administration (FDA)-approved artificial sweeteners include acesulfame-potassium, aspartame, neotame, saccharin, sucralose, and advantame (*High-Intensity Sweeteners*, n.d.). When artificial sweeteners were first FDA-approved, little attention was given to the potential long-term consequences of their consumption, including the risk of malignancy. Despite regulatory approval, concerns regarding the possible carcinogenicity of artificial sweeteners have persisted since the 1960s, when cyclamate was banned due to preliminary evidence of bladder cancer in rats. Although subsequent studies have not consistently replicated these findings, the incident underscores the importance of rigorous investigation into the long-term health effects of these widely consumed additives.

Over 95% of adults consume artificial sweeteners within their lifetime (Popkin & Nielsen, 2003). Many turn to artificial sweeteners as a measure against obesity and related diseases such as type 2 diabetes (Daher et al., 2022). The widespread adoption of artificial sweeteners has prompted researchers to examine the underlying health effects caused by consuming these low-calorie substitutes. To date, several artificial sweeteners have been linked to different cancers, however, the data remains contradictory and inconclusive (Arnold, 1983; Chi et al., 2018; Debras et al., 2022, 2022; Mann et al., 2000; Mukhopadhyay et al., 2000; Otabe et al., 2011; Schernhammer et al., 2012; Soffritti et al., 2006). This review aims to critically examine the evidence linking FDA-approved artificial sweeteners to cancer risk, highlighting areas for further research.

Methods

A systematic literature search was conducted using PubMed and Google Scholar, focusing on studies published between February 2018 and April 2024. The search terms included "non-nutritive sweeteners," "artificial sweeteners," "neoplasms," and specific names of the six

FDA-approved sweeteners. Studies in any language and with any study design were considered. Additional studies were identified through reference mining and expert recommendations.

Discussion

Aspartame

Aspartame was first approved by the FDA in 1974 (Nutrition, 2023). As a whole, aspartame remains one of the most studied artificial sweeteners to date (Nutrition, 2024). Studies linking artificial sweeteners and cancer predominantly evaluate aspartame, with data in both animal and human studies providing a range of connections to different carcinogens. Two studies suggest a link between aspartame consumption and the development of blood cancers such as leukemia and lymphoma (Schernhammer et al., 2012; Soffritti et al., 2006). In these studies, researchers treated mice with aspartame in their water, with a water-only group serving as a control (Dooley et al., 2017; EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS), 2013; Hagiwara et al., 1984). Across nearly 500 mice from these studies, researchers found similar findings, namely that the mice consuming aspartame had a higher risk of developing leukemia and lymphoma than the control mice. A similar experiment was conducted in rats, showing a sex-specific association between aspartame consumption and lymphoma development in male rats (Schernhammer et al., 2012).

Interestingly, a similar sex-specific finding occurred in a longitudinal human study assessing aspartame and the rate of lymphoma development. For this 22-year-long study, participants (N = 125,028) were asked to fill out a questionnaire about their aspartame use (focusing on diet sodas, the most popular mode of ingesting aspartame) and then personal medical history of malignancy. The study found a significant positive association between drinking one or more aspartame-sweetened sodas per day and a 30% increased risk of developing non-Hodgkin lymphoma in the male cohort. However, no significant association was found in the female cohort nor when all genders were combined and analyzed together. There was no clear reason for the difference in outcomes based on sex, though the results still do raise concerns about possible carcinogenic properties of aspartame (Schernhammer et al., 2012). Together, this preliminary evidence for increased carcinogenicity of aspartame in male mice and humans supports further research into the differential impact of aspartame based on biological sex.

Links between aspartame consumption and several other malignancies have been found in individual, small studies involving mice. This includes breast, liver,(Chi et al., 2018) lung, bladder, brain, and nerve cancer (Soffritti et al., 2006; Dooley et al., 2017; EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS), 2013). On the other hand, some small studies conducted on mice have found no link between aspartame and pancreatic, bladder brain, and liver cancers (Alkafafy et al., 2015; Ringel et al., 2022). The mixed findings of these small, animal-based studies warrant further investigation, especially in human subjects.

The impact of aspartame on carcinogenesis remains highly debated, most recently with the International Agency for Research on Cancer concluding that it is “possibly carcinogenic” (Nutrition, 2024). More data is needed to fully characterize aspartame’s impact on the risk of cancer development. Future areas of study should focus on expanding research to involve more

humans now that aspartame has been on the market and widely consumed for over four decades (Czarnecka et al., 2021). Overall, the evidence for aspartame's association with leukemia and lymphoma is the strongest and most well-studied. Several other studies have found mixed results with various other solid tumor types. While associations with cancer have been demonstrated, replication of these findings and additional research are required to establish conclusive claims.

Saccharin

Saccharin is a non-caloric sweetener used in many diet sodas and foods. Talks on cancer risk have been controversial for centuries. Existing studies on the carcinogenicity of saccharin are mainly focused on mice. While saccharin has been proven to induce higher rates of DNA damage compared to aspartame,(Bandyopadhyay et al., 2008) some studies failed to find a link between saccharin bearing any carcinogenic risk (Debras et al., 2022; *NHANES - About the National Health and Nutrition Examination Survey*, 2023; *NHANES III REFERENCE MANUALS AND REPORTS*, n.d.).

In 2023, a meta-analysis evaluating associations between endometrial cancer and consumption of artificial sweeteners, including saccharin, found no difference in the incidence rate of endometrial cancer between individuals exposed to artificial sweeteners and those who were not (Ringel et al., 2022). To our knowledge, no other studies on the association between endometrial cancer and saccharin exist at the time of this review (Li et al., 2024).

Three studies, taking place over two generations of mice, investigated the association between saccharin and bladder cancer and found that all showed that 5-7.5% sodium saccharin in diet from birth to death leads to increased bladder cancer rates, specifically in male mice (Armstrong & Doll, 1975; Hicks & Chowaniec, 1977; Kessler, 1976; Morgan & Jain, 1974)**.** These findings were supported by a toxicological and epidemiological study on mice, where they administered different doses of saccharin in mice into the mice's diet, and found a correlation between saccharin consumption and bladder cancer (Suez et al., 2015). Presently, there have been no human-based studies evaluating saccharin and bladder cancer.

Saccharin's increasing presence in daily diets contributes towards weight loss and helping diabetes makes it crucial that future areas of research should focus more on saccharin's effect on the carcinogenicity of other cancers linked to similar artificial sweeteners, such as its close relative aspartame's relation with leukemia, non-Hodgkin's lymphoma, and other related health issues.

Neotame

Neotame has been tested on several animal species, such as Sprague-Dawley rats, mice, beagle dogs, and New Zealand Rabbits (Chi et al., 2018). In a study with mice (N=10), clean water was administered to the control groups, and water containing neotame was administered to the treatment group for 4 weeks. Researchers found that mice consuming neotame had no difference in gut taxonomy or fecal metabolomes. Numerous sources have found neotame to be non-carcinogenic,(Nofre, 2000; Satyavathi et al., 2010) and safe in other health aspects as a diet additive (Chi et al., 2018). While neotame is a rarely used artificial sweetener compared to its competitors, future studies that reinforce its safety may lead the way for its broader use.

Acesulfame-Potassium

Acesulfame-Potassium (acesulfame-K) is a non-caloric sweetener around 120 times sweeter than sucrose and is highly water-soluble. Its structure is similar and comparable to aspartame. acesulfame-K is often blended with other sweeteners, such as sucralose or aspartame, to mask the bitter taste (Chattopadhyay et al., 2014). It is often used in a range of baked goods, gum, spreads, mouthwashes, and dairy products (*What Is Acesulfame Potassium, and Is It Good or Bad for You?*, 2020). Only one study in human adults (n=102,865) characterized the association of acesulfame-K and cancer and found it to increase cancer risk in a similar profile to that of aspartame, including various types of breast, prostate, and obesity-related cancers (Debras et al., 2022).

Another study conducted on albino Swiss mice aged 8-10 weeks found that a mixture of aspartame and acesulfame-potassium wasn't found to increase carcinogenicity or chromosomal abnormalities in the test group (Mukhopadhyay et al., 2000). Given the prevalent use of acesulfame-potassium in weight loss and diet culture. Future areas of research should aim to use acesulfame-k in experiments to search for cancers that other related sweeteners, such as aspartame and neotame, are subject to (Wilk et al., 2022).

Sucralose

Sucralose is an artificial form of the naturally occurring sugar, sucrose (AlDeeb et al., 2013). Most research on sucralose has been metabolic, studying the breakdown of sucralose into other non-toxic components, rather than clinical in animals or humans (A et al., 2000; Grice & Goldsmith, 2000; J et al., 2000; Sg et al., 2000). Over one hundred safety studies have been conducted testing the hydrolysis of sucralose, claiming sucralose is safe to consume in moderate amounts (Grice✠ & Goldsmith, 2000). Researchers found that 85% of sucralose was excreted intact; the other 15% doesn't interact with biological macromolecules and is biotransformed to biologically/toxicologically insignificant conjugates (Berry et al., 2016). Furthermore, the chemical structure of sucralose contains no structural alerts that give reason that it may promote carcinogenic activity, in part due to its chemical resemblance to sucrose (*Sucralose Non-Carcinogenicity: A Review of the Scientific and Regulatory Rationale*, n.d.). Even when exposure levels of sucralose are greatly magnified in rats, sucralose remains non-carcinogenic and safe to consume (Mann et al., 2000).

Advantame

Advantame is a relatively new artificial sweetener. It was approved by the FDA in 2014 and is similar in structure to neotame and aspartame. The few studies available characterizing the malignancy profile of advantame were all conducted on varying mammals (EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS), 2013; Otabe et al., 2011). Several genotoxicity assays - assays identifying possibly DNA-damaging substances - have been conducted in mice using advantame (EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS), 2013; Otabe et al., 2011). In the most significant and long-term study, N=384 mice underwent a 104-week dietary test and found no increased rates of tumor development or

neoplastic lesions (Otabe et al., 2011). The results of these studies in 2013 proved that advantame is both non-mutagenic and non-genotoxic. Future research should focus on human studies, as advantame is linked structurally to aspartame, which has been found to induce numerous cancers. As advantame continues to remain commercially available, the need for additional research grows.

Conclusion

While studies linking artificial sweeteners to cancer vary, the literature is still rudimentary, with few, high-quality, long-term, human-based studies to thoroughly evaluate the carcinogenic properties of artificial sweeteners. Most studies are small and provide only weak evidence of associations between cancers. As typical in biological research, most of what we know about the associations between artificial sweeteners and cancer risk are derived from animal models. Here, we include human data as available. Future human studies evaluating the association between artificial sweeteners and cancer risk are required. With brands such as such as *Splenda*, *Equal*, and *Truvia* becoming household staples, it is crucial to deepen our understanding of the long-term health implications of artificial sweeteners.

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