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An Analysis of the Link between Aspartame and Cancer and Its Public Health Implications

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Abstract

There have been conflicting reports that artificial sweeteners, including aspartame, increase the risk of malignancy despite their beneficial weight loss marketing. A literature review was conducted to determine the causality between aspartame and the incidences of cancer. Studies involving animals and humans were explored to determine the association and its impacts on the public health domain. Based on the current evidence, it appears that the link between aspartame and cancer is inconclusive at this time and that there seems to be no strong causality between the two factors. Future research should be directed at longer studies that are stronger in design to further explore the association between aspartame and cancer.

Introduction

America has a sweet tooth, and the sugar industry has generated billions of dollars in their contributions to baked goods, cooked items, desserts, and soft drinks. However, since the turn of the century, natural sugar products are slowly being replaced by artificial sweeteners as a more health conscientious option. Artificial sweeteners, or "sugar substitutes", are a group of agents that are synthetic sugar products, and some items on the market have a higher level of sweetness compared to natural sugar [1]. Currently, there are over 6 different types of artificial sweeteners used in approximately 17 trademarked sugar substitute products including popular products such as Splenda, Sweet N' Low, and Equal. Manufacturers are currently reviewing other novel artificial sweeteners for distribution onto the United States market.

The popularity of artificial sweeteners occurred in the 1880s as the rates of obesity, cardiovascular disease, and diabetes started to rise [1]. One of the benefits of artificial sweeteners is that they have minimal contributions to sugar levels and are weight neutral. As a result, these sugar substitutes have been recommended by the medical community as a more attractive option for those with metabolic syndrome or obesity. For example, the American Diabetes Association recommends that people with diabetes substitute natural sugar products with artificial sweeteners to lower the risk of hyperglycemia and to help aid in further weight loss [2]. Additionally, artificial sweeteners have been a health food craze as people are ingesting it to reduce weight and lower their daily caloric content. Despite the health benefits of artificial sweeteners, there have also been many reports of negative side effects with its usage including abdominal pain, diarrhea, and most alarmingly, cancer.

The Food and Drug Administration (FDA) is responsible for the regulation of artificial sugar products as a food additive. However, unlike other food additives, approval for the United States market is not governed by the FDA because it is under the category "Generally Recognized as Safe" (GRAS) [1]. As a result, scientists marketing the artificial sweetener only need to show that it is safe through toxicology tests comparing it to other similar products available on the market. The FDA does not need to be notified of the product if the manufacturer launches it onto the public domain so long as it does not cause harm in the consumer. There are six artificial sweeteners on the United States market: saccharin, aspartame, acesulfame potassium (Ace-K), sucralose, neotame, and advantame.

One of the first artificial sweeteners discovered was saccharin. While saccharin was marketed with a 200-700 times sweeter intensity compared to sucrose, it quickly stirred controversy as it was linked to bladder cancer in rats [3].

Other sugar substitutes approved after saccharin showed similar results. In 1981, aspartame was approved as a sugar substitute and has currently been one of the most commonly used artificial sweeteners to date. It has been included as an active ingredient in sugar packets, syrups, dairy

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products, desserts, and beverages. In the body, aspartame is broken down into two amino acids, aspartate and phenylalanine, and methanol [4]. Methanol can be further converted in the body into formaldehyde, a chemical commonly found in preserving fluid and is a known carcinogen. There have also been reports of toxicity with the ingestion of the aspartame products. Despite this, aspartame is found in over 6,000 types of foods and marketed in 90 countries across the world [5].

While there has been much evidence regarding the benefits of artificial sweeteners on weight loss and glucose stability, there have also been reports that these products may cause harm. There have been conflicting reports that some artificial sweeteners may predispose or increase the risk of malignancy in consumers. This paper looks to determine the causality between aspartame, one of the most studied artificial sweeteners on the market, and the rates of cancer.

Materials and Methods

A literature search was conducted on PUBMED and MEDLINE databases using search terms involving "aspartame", "artificial sweeteners", and "cancer. Studies involving animals and humans were explored to determine the association and its impacts on the public health domain.

Results and Discussion

Studies of aspartame in animals

There have been three studies in animals that have shown a positive association between aspartame and cancer. Soffritti et al. [6] in 2006 showed that mice feeding on aspartame had an increased rate of lymphomas, leukemia, and renal pelvis carcinomas [6]. In 2007, Soffritti et al. [7] performed a similar study on 95 rats and found a higher rate of cancer in rats taking greater than 2,000 ppm [7]. In 2010, Soffritti et al. also showed higher rates of alveolar and bronchiolar carcinomas especially in rats taking 32,000 ppm of aspartame [8]. However, these early studies were critiqued since they used sicker rats in the study at baseline. Studies after these did not show causality between aspartame intake and cancer. Searle et al. completed a carcinogen assay test on 60 mice for duration of 104 weeks and found no difference in the malignancy rates between controls and the aspartame group [9]. Similarly, in the National Toxicology Program, mice that were fed aspartame did not have a higher rate of papillomas, lymphomas, or brain tumors compared to controls at 40 weeks [9]. Additionally, the study by Ishii et al. on 86 rats found no difference in the rates of brain tumors at 104 weeks [9].

Studies of aspartame in humans

An epidemiological study on the rates of brain cancer from 1972-1992 in the National Cancer Institute's Surveillance Epidemiology and Ends Results (SEER) Program hypothesized that aspartame may be linked to the results [10]. Looking at the data in 1985, there was a steep rise in the brain cancer rates in young adults that were found in the study, and the authors concluded that these rates coincided with the approval of aspartame on the market. The authors also made their conclusion from the studies of aspartame in rats causing malignant brain tumors and suggested the correlation.

Additionally, a cohort study was conducted on 1,324 patients in the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS) by Schernhammer et al. [11] over duration of 22 years where information about aspartame intake was obtained through study questionnaires on dietary intake [11]. While men who ingested diet soda had an increase in the rates of non-Hodgkin lymphoma, (RR: 1.31; 95% CI: 1.01, 1.72), the link was not statistically significant with an analysis of both genders (RR 1.13; 95% CI 0.94 – 1.34; P = 0.24). There were no differences in the rates of leukemia for those receiving aspartame in their diet (RR 1.42, 95% CI 1.00-2.02; P = 0.93). However, the association was stronger for multiple myeloma in men (RR 2.02; 95% CI 1.2-3.4; P = 0.01). There was also higher incidence of multiple myeloma in patients ingesting aspartame on a daily basis, however (RR 1.29; 95% CI 0.89 – 1.89; P = 0.04).

Likewise, the case-control study of 532 patients with pancreatic cancer by Chan et al. also showed that men had a higher risk of cancer while on artificial sweeteners [12]. This was seen in men who ate sweets containing sugar substitutes (OR 1.9; 95% CI 1.0-3.6; P = 0.01), especially if they ate mixed candy bars (OR 3.3; 95% 1.5-7.3; P = 0.001) or sweet condiments (OR 1.9; 95% CI 1.2-3.1; P = 0.002). This trend was not seen among women. Additionally, while the link of pancreatic cancer was not seen in both genders who consumed overall sweetened beverages (OR 1.0; 95% CI 0.7-1.3; P = 0.07), both genders had higher rates of cancer if they consumed Hawaiian punch, lemonade, or fruit drinks with sugar substitutes (OR 1.0; 95% CI 0.6-1.8; P = 0.03). The study did not reveal the percentage of patient's solely consuming aspartame as the sugar substitute.

In the study conducted by Lim et al, approximately 500,000 patients in the NIH-AARP Diet and Health Study cohort were analyzed using baseline questionnaires about aspartame-containing foods and beverages that were originally mailed out to study participants [13]. Cancer cases were identified using ICD codes from cancer registries and at 5.2 years, there were 1,888 cases of hematopoietic cancers and 315 case malignant gliomas among study subjects. However, aspartame was not linked with gliomas (RR 0.73, 95% CI 0.45-1.15, P = 0.05), gliobastomas (RR 0.64, CI 0.37-1.10; P = 0.05), or lymphoid cancers (RR 0.95, 95% CI 0.70-1.29, P = 0.91). There was also no correlation that higher doses of aspartame caused more cancer rates.

In the study by McCullough et al, approximately 100,000 patients followed over a period of 10 years in the CPS-II Nutrition Cohort with a 152-item questionnaire containing information about soda intake containing artificial sweeteners [14]. There results revealed that those who continuously consumed at least one can of soda per day had no increase in non-Hodgkin's lymphoma (RR 1.00, 95% CI 0.98-1.03, P = 0.62) after it was adjusted for confounders. Additionally, those who had a continuous intake of aspartame defined in the study as greater than 50 mg per day also did not have a higher risk of non-Hodgkin's lymphoma (RR 0.99, 95% CI 0.95 - 1.03; P = 0.69).

A case-control study conducted on 230 patients in Italy by Bosetti et al. [15] revealed that patients using low-calorie sweeteners including aspartame did not have higher rates of gastric cancers (OR 0.8; 95% CI 0.45 - 1.45), pancreatic cancers (OR 0.62, 95% CI 0.37-1.04), or endometrial cancers (OR 0.96; 95% CI 0.67 - 1.40) [15]. However, the study did not reveal the portion of patients who consumed aspartame compared to other types of sugar substitutes, although it was mentioned that aspartame is consumed higher in Italy than other products.

Another case-control study by Gurney et al. [16] on 56 pediatric subjects born after 1981 revealed that the rates of brain tumors did not increase (OR 1.1, 95% CI 0.5 - 2.6) for those consuming aspartame [16]. Additionally, there was no correlation between the age of first consumption (OR 1.0; 95% CI 0.3-3.1), duration of consumption (OR

1.2; 95% 0.4 - 3.3), or frequency of consumption (OR 1.6; 95% CI 0.5 - 5.2) of aspartame with cancer. The study also studied the placenta transfer of aspartame in pregnant mothers and showed no increase in brain tumors (OR 0.7, 95% 0.3-1.7) for all trimesters of pregnancy as well as no correlation for females consuming aspartame while breastfeeding (OR 1.1; 95% CI 0.3-4.0).

Finally, the study by Gallus et al. was a case-control study in Italy in 598 patients between 1991 - 2004 [17]. Among the cases that used artificial sweeteners, with the majority of it being aspartame, the rates of oral cancer (OR 0.77; 95% CI 0.39 - 1.53), colon cancer (OR 0.90; 95% CI 0.7 - 1.16), breast cancer (OR 0.8; 95% CI 0.65 - 0.97), ovarian cancer (OR 0.75; 95% CI 0.56-1.00), prostate cancer (OR 1.23; 95% CI 0.86-1.76), and renal cell carcinoma (OR 1.03; 95% CI 0.73 - 1.46) were not statistically significant. The results were also not statistically different among patient factors such as high body-to-mass ratios, gender, or age.

Discussion and current gaps

The results of cancer occurrences in patients consuming aspartame are conflicting. While animal studies have generally resulted in a lack of causality for cancer and aspartame, the evidence in humans is less clear cut. However, there are many limitations to all of the studies that were conducted. There have been no randomized controlled studies in humans and most of the evidence in this topic comes from observational or cohort studies. With these trial designs, the association between cancer and aspartame is weak. There are many confounders that might have skewed the study results. For instance, in studies social factors such as tobacco usage or alcohol intake can affect cancer incidences, are not taken into account [10,11,16]. Additionally, all of the studies presented do not control for environmental exposures such as asbestos, sun exposure, radon, benzene, or pollution as sources of cancer. There might be genetic factors in the subjects that might have predisposed them to getting cancer in the study, and lifestyle modifications such as diet or exercise was not accounted for in most studies. In only studies, were body-to-mass ratio controlled as a confounder, and there is no mention of refined foods or red meat intake in these studies as a possible source of bias [14,15,17].

Another limitation of these studies is that the dosage of aspartame ingested was not standardized between the trials. For example, in McCullough et al., subjects drank on average just one can of soda a day, but in Lim et al. [13] some subjects drank five cans a day [13,14]. Other studies such as Bosetti et al. [15] did not reveal how much aspartame the patients ingested [15]. Additionally, studies measured aspartame intake as either from candy sources as in the case of Chan et al. [12] or as soda or fruit drink sources, or from packet sources like in Lim et al. [12,13]. With the inconsistencies between the studies, it becomes difficult to finalize a numerical value for aspartame and cancer. The FDA's recommended Acceptable Daily Intake (ADI) for aspartame is 50 mg/kg of body weight [18]. According to the ADA, it would take 17 cans of diet soda or 97.4 packets of sugar substitutes to reach the ADI for aspartame [18]. However, in studies such as, some patients had a heightened risk of cancer at amounts well below the ADI recommended by the FDA [11,12]. There have been no studies in humans that have used aspartame doses that are close to or higher than the FDA's ADI.

Also, depending on the cancer type or location, it may take as long as 10 years for the tumor to grow before it is diagnosed [3]. The study by Schernhammer et al. [11] seems to have the longest duration, pooling the data for 22 years compared to Chan et al with a 5 year analysis [11,12]. The studies also relied on ICD codes for diagnosis such as Lim et al. [13] and it is unclear if the diagnostic imaging tests such as CT scan, ultrasound, or biopsies were correct with the diagnoses. The Delaney Clause was passed as part of the Food Additives Amendment in 1958 where additives that are shown to be carcinogenic are prohibited to be on the market [19]. However, since of the conflicting evidence in the studies with aspartame, it makes it difficult to determine if aspartame is a violation of the Delaney Clause. Additionally, another weakness of these studies was that there were some types of cancer that have not been studied such as hepatic, thyroid, lung, or skin cancer. Perhaps if these types of cancers were studied or if the duration of time of the studies was extended, the results might have led to a positive diagnosis.

Conclusion

Based on the current evidence, it appears that the link between aspartame and cancer is inconclusive at this time and that there seems to be no strong causality between the two factors. As a result, it is important to adhere to the FDA's recommendations of the 50 mg/kg ADI for aspartame to minimize the toxicities of its usage. It is also noteworthy to mention that one can also consider natural sources of sugar as an alternative to artificial sweeteners for health benefits. For example, honey has high levels of sucrose with antioxidant properties. Additionally, fruits contain natural sources of sugar and possess no dietary harms.

Future research should be directed at longer studies that are stronger in design to further explore the association between aspartame and cancer. Additionally, studies can be done on special populations such as patients who have a past history of cancer or those with diabetes who use aspartame as a low-calorie alternative. Finally, it might be beneficial to revisit the Delaney Clause and impose a time frame and dosage equivalent for the additive and cancer. For example, since there has been no standardization between how long studies have to show the association for cancer or at what equivalent human dosage, policy changes to develop guidelines and protocols in this area would help make the data more validated and reliable for future additives. Policy should also delay the approval of a new additive on the market until these tests are completed.

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