Consumption of Aspartame-Containing Beverages and Incidence of Hematopoietic and Brain Malignancies

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Abstract

Background: In a few animal experiments, aspartame has been linked to hematopoietic and brain cancers. Most animal studies have found no increase in the risk of these or other cancers. Data on humans are sparse for either cancer. Concern lingers regarding this widely used artificial sweetener.

Objective: We investigated prospectively whether aspartame consumption is associated with the risk of hematopoietic cancers or gliomas (malignant brain cancer).

Methods: We examined 285,079 men and 188,905 women ages 50 to 71 years in the NIH-AARP Diet and Health Study cohort. Daily aspartame intake was derived from responses to a baseline self-administered food frequency questionnaire that queried consumption of four aspartame-containing beverages (soda, fruit drinks, sweetened iced tea, and aspartame added to hot coffee and tea) during the past year. Histologically confirmed incident cancers were identified from eight state cancer registries. Multivariable-adjusted relative risks (RR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression that adjusted for age, sex, ethnicity, body mass index, and history of diabetes.

Results: During over 5 years of follow-up (1995-2000), 1,888 hematopoietic cancers and 315 malignant gliomas were ascertained. Higher levels of aspartame intake were not associated with the risk of overall hematopoietic cancer (RR for ≥600 mg/d, 0.98; 95% CI, 0.76-1.27), glioma (RR for ≥400 mg/d, 0.73; 95% CI, 0.46-1.15; P for inverse linear trend = 0.05), or their subtypes in men and women.

Conclusions: Our findings do not support the hypothesis that aspartame increases hematopoietic or brain cancer risk. (Cancer Epidemiol Biomarkers Prev 2006;15(9):1654–9)

Introduction

Aspartame has been the predominant artificial sweetener in the U.S. for the past 25 years and is currently found in >6,000 food and beverage products (1). Throughout this period, however, there has been a controversy regarding whether or not aspartame is carcinogenic (2).

Speculation about an association between aspartame and brain cancer risk was raised in an article (3) which temporally linked increasing incidence rates in the U.S. during the period from 1975 to 1992, especially an upward shift of more aggressive glioblastomas during the 1980s, to the entry of aspartame in the food supply in 1981. The authors cited data from an earlier positive animal study reviewed by the Food and Drug Administration (4) and an in vitro nitrosation experiment (5) to support their hypothesis. The article was later criticized for committing ecological fallacy, wherein the temporal coincidence of two events observed at an ecological level without examination of individual data can lead to faulty conclusions regarding risk association (6), and the supporting evidence cited for the article was also refuted (7, 8). More recent and extensive animal trials have failed to show the carcinogenic activity of aspartame (1, 9-11). Additionally, a population-based case-control study found a null association between childhood brain tumors and aspartame intake among both children and their mothers during pregnancy and lactation (12). In contrast, however, a recent study found that female rats fed aspartame developed more lymphomas and leukemias than controls, in a dose-dependent manner, starting from a dose that may be relevant to human intake (as low as 20 mg per kg body weight; refs. 13, 14), which is lower than the acceptable daily intake established by the Food and Drug Administration at 50 mg per kg body weight (1). This study, compared with previous ones, had a large sample size (~1,800 rats) and was observed over a life span (13, 14).

Given the recent finding of an association between aspartame and hematopoietic cancers in rats, and past concerns about an association with brain cancers, we undertook a study to assess this relationship in a large prospective study of humans. We investigated the association between self-reported consumption of aspartame-containing beverages and incident hematopoietic and brain cancers in the prospective NIH-AARP Diet and Health Study.

Materials and Methods

The NIH-AARP Diet and Health Study. The NIH-AARP Study was carried out by the National Cancer Institute to investigate the relationship between diet and health. The details of the study have been described previously (15). Briefly, 3.5 million baseline questionnaires were mailed from 1995 to 1996 to members of the AARP who were 50 to 71 years old and resided in one of eight study areas (California, Florida, Pennsylvania, New Jersey, North Carolina, Louisiana, and metropolitan Atlanta and Detroit). Out of 617,119 questionnaires returned, 567,169 were satisfactorily completed (15). We excluded 1 withdrawal, 179 duplicates, 582 persons who had died or moved out of the study area before study entry, 52,887 persons with history of cancer (to avoid spurious associations due to life-style changes after diagnosis) or with only death reports of cancer, 15,760 proxy responders, 4,399 persons who were outliers on reported energy intake, and...
19,377 persons with missing or outlier values of body mass index (BMI: weight in kilograms/height in meters squared) or with BMI <18.5 (<1% of study population; to avoid unreliable questionnaire responses in general). As a result, we considered 473,984 questionnaires (from 285,079 men and 188,905 women) for the current study. The NIH-AARP Study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute.

Cancer Outcome Ascertainment. Histologically confirmed incident cancer cases were ascertained from the eight state cancer registries up to December 31, 2000 (16). A validation study showed that our methods identified 90% of all incident cancer cases within these eight state cancer registries (16). Based on the pertinent case information (International Classification of Disease-Oncology; ICD-O) and the WHO classification (17), we classified cancer of the hematopoietic system (9-13). We excluded non-malignant cases (14), non-Hodgkin lymphoma, and multiple primary cancers.

Table 1. Baseline age-adjusted characteristics (means and proportions) by aspartame intake levels derived from aspartame-containing beverages, the NIH-AARP Diet and Health Study, 1995-2000 (N = 473,984)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Overall</th>
<th>Aspartame intake (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort participants (%)</td>
<td>100</td>
<td>46 25 13 7 5 4</td>
</tr>
<tr>
<td>Aspartame (mg/d) [among users only]</td>
<td>111 [205]</td>
<td>0 47 147 267 441 986</td>
</tr>
<tr>
<td>Age at entry</td>
<td>62.0</td>
<td>62.2 62.5 61.9 61.4 60.7 59.9</td>
</tr>
<tr>
<td>Sex (%) women</td>
<td>40</td>
<td>38 44 42 41 35 34</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td>Non–Hispanic White 91 90 92 93 94 95 94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non–Hispanic Black 74 37 42 41 39 40 34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others 5 6 5 4 3 3 3</td>
</tr>
<tr>
<td>Education (%)</td>
<td>&lt;12</td>
<td>6 7 5 5 6 5 7</td>
</tr>
<tr>
<td></td>
<td>12-15</td>
<td>52 53 51 51 53 52 57</td>
</tr>
<tr>
<td></td>
<td>16-18</td>
<td>39 37 42 41 39 40 34</td>
</tr>
<tr>
<td></td>
<td>Error or missing responses</td>
<td>3 3 3 3 3 3 3</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>9</td>
<td>3 9 14 19 22 26</td>
</tr>
<tr>
<td>Family history of cancer (%)</td>
<td>49</td>
<td>48 49 49 50 49 48</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>12</td>
<td>14 12 11 10 11 13</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>Never</td>
<td>36 36 37 35 33 31 29</td>
</tr>
<tr>
<td></td>
<td>Former</td>
<td>51 47 53 55 56 58 57</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>12 15 9 9 10 10 13</td>
</tr>
<tr>
<td></td>
<td>Error or missing responses</td>
<td>2 2 2 2 1 2 1</td>
</tr>
<tr>
<td>BMI</td>
<td>≥18.5, &lt;25 (%)</td>
<td>35 42 33 29 24 21 19</td>
</tr>
<tr>
<td></td>
<td>≥25, &lt;30</td>
<td>43 42 44 46 45 45 42</td>
</tr>
<tr>
<td></td>
<td>≥30, &lt;35</td>
<td>16 13 16 19 22 23 26</td>
</tr>
<tr>
<td></td>
<td>≥35</td>
<td>6 4 6 7 9 10 13</td>
</tr>
<tr>
<td>Physical activity (%)</td>
<td>≤3-4 /mo</td>
<td>31 32 29 29 31 32 37</td>
</tr>
<tr>
<td></td>
<td>≤1-2 /wk</td>
<td>22 22 22 22 22 21 19</td>
</tr>
<tr>
<td></td>
<td>≥3-4 /wk</td>
<td>46 45 49 48 47 45 43</td>
</tr>
<tr>
<td>Calories (kcal)</td>
<td>1,835</td>
<td>1,919 1,692 1,734 1,844 1,855 2,044</td>
</tr>
<tr>
<td>Caffeine (mg/d)</td>
<td>366</td>
<td>393 321 336 367 364 424</td>
</tr>
<tr>
<td>Daily frequency (serving/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet soda</td>
<td>0.4</td>
<td>— 0.2 0.6 0.9 2.2 3.5</td>
</tr>
<tr>
<td>Diet fruit drinks</td>
<td>0.05</td>
<td>— 0.03 0.1 0.2 0.1 0.2</td>
</tr>
<tr>
<td>Diet iced tea</td>
<td>0.1</td>
<td>— 0.1 0.2 0.4 0.2 0.3</td>
</tr>
<tr>
<td>Aspartame in coffee/hot tea</td>
<td>0.3</td>
<td>— 0.2 0.6 1.2 0.6 0.6</td>
</tr>
</tbody>
</table>

NOTE: General linear regression model was used to estimate age-adjusted means of variables for each aspartame intake level.


Table 2. Adjusted RRs and 95% CIs of incident hematopoietic cancers and malignant gliomas according to aspartame intake levels derived from aspartame-containing beverages, the NIH-AARP Diet and Health Study, 1995-2000 (n = 473,984)

<table>
<thead>
<tr>
<th>Aspartame intake (mg/d)</th>
<th>All hematopoietic cancers</th>
<th>Gliomas*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men and women combined</td>
<td>Men</td>
</tr>
<tr>
<td>Case, Person-years</td>
<td>RR (95% CI)</td>
<td>Case, Person-years</td>
</tr>
<tr>
<td>None</td>
<td>869 946,316 1.00 (Referent)</td>
<td>615 585,965 1.00 (Referent)</td>
</tr>
<tr>
<td>&gt;0, &lt;100</td>
<td>432 505,228 0.91 (0.81-1.03)</td>
<td>294 279,047 0.95 (0.83-1.10)</td>
</tr>
<tr>
<td>≥100, &lt;200</td>
<td>280 274,430 1.10 (0.96-1.26)</td>
<td>187 158,731 1.09 (0.92-1.29)</td>
</tr>
<tr>
<td>≥200, &lt;400</td>
<td>157 148,017 1.01 (0.84-1.21)</td>
<td>95 86,800 1.03 (0.83-1.29)</td>
</tr>
<tr>
<td>≥400, &lt;600</td>
<td>104 109,262 1.05 (0.85-1.29)</td>
<td>76 70,059 1.07 (0.84-1.36)</td>
</tr>
<tr>
<td>≥600</td>
<td>66 77,357 0.98 (0.76-1.27)</td>
<td>51 49,960 1.06 (0.79-1.42)</td>
</tr>
<tr>
<td>P for trend</td>
<td>—</td>
<td>0.56</td>
</tr>
</tbody>
</table>

NOTE: Cox proportional hazards regression model adjusted for age at entry (continuous), sex (for combined analysis), ethnicity (non–Hispanic White, non–Hispanic Black, others), BMI (weight in kilograms/height in meters squared; 4 categories of ≥18.5 and <25, ≥25 and <30, ≥30 and <35, and ≥35), and history of diabetes.

*Due to small numbers, aspartame categories of’’≥400, <600’’ and’’≥600’’ were collapsed for gliomas.


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Table 3. Adjusted RRs and 95% CIs of incident subtype hematopoietic cancers according to aspartame intake levels derived from aspartame-containing beverages, the NIH-AARP Diet and Health Study, 1995-2000 (n = 473,984)

<table>
<thead>
<tr>
<th>Aspartame intake (mg/d)</th>
<th>Hodgkin lymphoma</th>
<th>Multiple myeloma</th>
<th>Lymphoid malignancies*+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case, N = 57</td>
<td>RR (95% CI)</td>
<td>Case, N = 273</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>None</td>
<td>29</td>
<td>1.00 (--, 0.62-1.17)</td>
<td>127</td>
</tr>
<tr>
<td>&gt;0, &lt;100</td>
<td>28</td>
<td>0.77 (0.44-1.32)</td>
<td>57</td>
</tr>
<tr>
<td>≥100, &lt;200</td>
<td>48</td>
<td>1.39 (0.99-1.96)</td>
<td>177</td>
</tr>
<tr>
<td>≥200, &lt;400</td>
<td>20</td>
<td>1.13 (0.70-1.83)</td>
<td>92</td>
</tr>
<tr>
<td>≥400, &lt;600</td>
<td>21</td>
<td>1.03 (0.64-1.66)</td>
<td>45</td>
</tr>
<tr>
<td>≥600</td>
<td>45</td>
<td>0.95 (0.70-1.29)</td>
<td></td>
</tr>
</tbody>
</table>

P for trend 0.34 0.40 0.91

NOTE: Cox proportional hazards regression model adjusted for age at entry (continuous), sex, and ethnicity (non–Hispanic White, non–Hispanic Black, others); BMI (weight in kilograms / height in meters squared; four categories of ≥18.5 and <25, ≥25 and <30, ≥30 and <35, and ≥35), and history of diabetes.

*The aspartame-cancer associations are presented separately for lymphoid malignancies and non–lymphoid leukemias, then main lymphoid malignancies of Hodgkin lymphoma, multiple myeloma, and non-Hodgkin lymphoma. In addition, two subgroups within non-Hodgkin’s lymphoma are presented: (a) small lymphocytic lymphoma and chronic lymphocytic leukemia and (b) immunoblastic lymphoma and lymphoblastic leukemia.

† Due to small numbers, higher aspartame categories were collapsed for subtype cancers other than non-Hodgkin lymphoma.

Participants were also queried regarding the consumption of aspartame added to cups of coffee and hot tea. From these responses, we computed daily consumption of aspartame, taking into account aspartame content, portion size, and intake frequency of each beverage: the aspartame content per 100 g beverage was estimated to be 50 mg for diet soda (i.e., 180 mg/12 oz can), 14.95 mg for diet fruit drink, 25.55 mg for diet iced tea, and 35 mg (per tabletop packet) for the addition to each cup of coffee/hot tea based on the information provided by the Nutrition Data System for Research (University of Minnesota http://www.ncc.umn.edu/) and the literature (21).

Statistical Analysis. We computed standardized incidence ratios (SIR) to compare the incidence rates in the NIH-AARP Study with the rates in the U.S. Surveillance, Epidemiology, and End Results data (22). For this comparison only, and not for the rest of the analyses, we included all individuals, regardless of history of other cancers. The SIRs standardized for age, gender, and ethnicity were estimated for overall hematopoietic cancers and malignant gliomas using SEER*Stat software (version 6.2.3). We estimated minimal detectable relative risk (RR) of hematopoietic and brain cancers using Power software (version 3.0.0; ref. 23), given the cohort design/size, number of cases, and post hoc exposure/disease probabilities for a comparison of +600 mg/d versus none with a two-sided α level at 0.05 and 80% power.

Baseline characteristics were examined according to increasing levels of aspartame intake (Table 1). A general linear regression model was used to estimate age-adjusted means of baseline characteristics for each intake level of aspartame. Multivariable-adjusted RR and 95% confidence intervals (CI) for the association between aspartame and hematopoietic and brain cancers were estimated using Cox proportional hazards regression with the follow-up time as time metric and with adjustments for age at study entry, sex, and ethnicity (non–Hispanic White, non–Hispanic Black, and others; Tables 2 and 3). Among the baseline characteristics we examined as potential confounders in Table 1, we adjusted for BMI (four categories of ≥18.5 and <25, ≥25 and <30, ≥30 and <35, and ≥35) and history of diabetes, because they attenuated the association between aspartame and non–lymphoid leukemias by ≥10%. Linear trends between aspartame intake categories and cancer (dose-response) were determined using the two-sided Wald test of a score variable that contained median values of the categories. Effect modification was evaluated using cross-product terms (P < 0.10 was considered significant) and likelihood ratio test statistics comparing models with...
and without a product term. Statistical analyses were conducted using the SAS software systems (version 8, SAS Institute, Cary, NC). All $P$ values were two-sided and were considered statistically significant at an $\alpha$ level of $<0.05$.

**Results**

After following up 473,984 persons without history of any prior cancer for up to 5.2 years (up to 75 years of age, median 67) with 2,060,611 person-years, 1,318 men and 570 women were diagnosed with incident hematopoietic cancers and 225 men and 90 women with malignant gliomas. The incidence rates in the NIH-AARP Study were largely comparable to the Surveillance, Epidemiology, and End Results rates for overall hematopoietic cancers [SIR for age-standardized rate among Whites in the NIH-AARP Study (102/100,000 person-years), 0.89; 95% CI, 0.85-0.93] and gliomas (SIR for 16/100,000 person-years, 0.99; 95% CI, 0.88-1.10), which were similar in men and women. SIRs in other races were similar to those for Caucasians in magnitude and not significantly different from null (data not shown).

Table 1 shows baseline characteristics and daily frequency of aspartame-containing beverages by level of aspartame intake. Users of aspartame-containing beverages consumed $\sim200$ mg of aspartame daily ($\sim$ one 12-oz can of diet soda). Among the consumers of aspartame, people with higher intakes were likely to be younger, to be men, to have more frequent history of smoking, to be less physically active, and to have higher caloric and caffeine intakes (Table 1). Overall, compared with people who did not consume aspartame, people with increasing levels of aspartame intake were likely to have a history of diabetes and higher BMI. The trends for ethnicity, education, family history of cancer, and intake of alcohol were not consistent with increasing intake of aspartame.

Compared with no consumption of aspartame, increasing levels of consumption were not associated with any risk of overall hematopoietic cancer (Table 2: adjusted RR for $\geq 600$ mg/d versus none, 0.98; 95% CI, 0.76-1.27; $P$ trend = 0.56), in men or women. Aspartame was also not associated with gliomas, overall (RR $\geq 400$ mg/d versus none, 0.73; 95% CI, 0.46-1.15; $P$ trend = 0.05) or in glioblastomas, the largest subtype ($n = 231$; RR, 0.64; 95% CI, 0.37-1.10; $P$ trend = 0.05). The associations were similarly null when the lowest level of aspartame intake was set as the reference category. A more detailed categorization of aspartame intake did not indicate an elevated cancer risk associated with higher levels of intake [data not shown; hematopoietic cancer RR for $\geq1,200$ mg/d ($n = 12$ cases) versus none, 0.85; 95% CI, 0.48-1.50; glioma RR for $\geq1,200$ mg/d ($n = 3$ cases) versus none, 1.15; 95% CI, 0.36-3.64].

The association remained null for the main subtypes of lymphoid cancers (Hodgkin lymphoma, multiple myeloma, and non–Hodgkin lymphoma; Table 3). Specifically, the non–Hodgkin lymphoma subtypes (small lymphocytic lymphoma and chronic lymphocytic leukemia, immunoblastic lymphoma, and lymphoblastic lymphoma/leukemia) and non-lymphoid leukemias that were found more frequently in the aspartame treatment group of a recent animal study (13) did not show any association with aspartame intake (Table 3). These findings did not change materially (i.e., changed $<10\%$) with further adjustments for education, family history of cancer, alcohol, smoking history, physical activity, calories, caffeine, and other dietary and life-style risk factors and did not vary by gender or age ($<60$ versus $\geq60$ years).

**Discussion**

To our knowledge, this study is the first investigation of aspartame and hematopoietic cancers in humans. Our findings of no increased risk of brain cancer, although limited to malignant gliomas, are consistent with the majority of animal studies (7-9, 11) and a human case-control study on brain cancer (12): the protective association between aspartame and gliomas may be due to chance or residual confounding by other dietary/life-style factors, as suggested by another finding of an inverse association of diet soda for esophageal adenocarcinoma (24). Our findings are in direct contradiction with a recent rat study that claimed carcinogenicity of aspartame in hematopoietic, nervous, and other systems (13, 14). A thorough review of this animal study by the European Food Safety Authority (25), however, dismissed the findings because of unusually high background chronic inflammatory conditions in the rats and the fact that there were no indications of a dose-response among other issues.

Our study has a number of strengths. Because of its large size, we could examine relatively rare subtypes of hematopoietic and brain cancers and we had sufficient power ($80\%$) to detect a moderate association of 600 mg/d or more of aspartame with overall hematopoietic cancer (RR $>1.24$), non–Hodgkin lymphoma subtypes and non-lymphoid leukemia (RR $>1.37$), and gliomas (RR $>1.52$). Data collection of dietary and life-style factors prior to diagnosis minimizes bias due to differential reporting between cases and controls. The study ascertained histologically confirmed incident cases from eight cancer registries with $\sim90\%$ completeness (15, 16), indicating that null findings are not likely due to misclassification of cases. Our multivariate analyses suggested that the observed null associations were not confounded by an array of dietary or life-style risk factors examined.

The NIH-AARP FFQ was developed through extensive cognitive testing (26-28) and was validated against two 24-hour

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**Table 3. Adjusted RRs and 95% CIs of incident subtype hematopoietic cancers according to aspartame intake levels derived from aspartame-containing beverages, the NIH-AARP Diet and Health Study, 1995-2000 ($n = 473,984$) (Cont’d)**

<table>
<thead>
<tr>
<th>Non–Hodgkin lymphoma</th>
<th>Non–lymphoid leukemia*+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small lymphocytic lymphoma and</strong></td>
<td><strong>Immunoblastic lymphoma and</strong></td>
</tr>
<tr>
<td><strong>chronic lymphocytic leukemia</strong></td>
<td><strong>lymphoblastic lymphoma/leukemia</strong></td>
</tr>
<tr>
<td><strong>Case, N = 241</strong></td>
<td><strong>Case, N = 45</strong></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>1.00 (—)</td>
<td>1.00 (—)</td>
</tr>
<tr>
<td>1.03 (0.75-1.41)</td>
<td>0.77 (0.42-1.42)</td>
</tr>
<tr>
<td>1.16 (0.79-1.71)</td>
<td>1.02 (0.69-1.52)</td>
</tr>
<tr>
<td>0.84</td>
<td>0.40</td>
</tr>
<tr>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td>1.00 (—)</td>
<td>1.00 (—)</td>
</tr>
<tr>
<td>0.93 (0.68-1.27)</td>
<td>0.93 (0.68-1.27)</td>
</tr>
<tr>
<td>1.31 (0.93-1.85)</td>
<td>1.31 (0.93-1.85)</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>1.05 (0.65-1.70)</td>
<td>1.05 (0.65-1.70)</td>
</tr>
<tr>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>1.25 (0.82-1.91)</td>
<td>1.25 (0.82-1.91)</td>
</tr>
</tbody>
</table>
dietary recalls (15), indicating that it is of similar high quality to other FFQs being used in prospective cohorts in the U.S. As in other prospective cohorts (29-32), we queried food consumption over the previous year to maximize the recall accuracy, and at the same time, capture seasonal variation (33). Most etiologic prospective studies, in using FFQs, aim to rank individuals on food/nutrient intakes rather than to estimate absolute amounts (33). FFQs, however, are known to contain a substantial amount of measurement error as evidenced by studies using recovery biomarkers of protein and energy intakes (34, 35). Such findings suggest that results for diet and chronic disease associations may be substantially attenuated due to measurement error (36, 37). Although validation studies of FFQs against diet records show higher correlations for beverages (38) and low-calorie carbonated beverages \((r \approx 0.73; \text{ref. 39})\) than for other food items, we cannot rule out the possibility that the reporting error in the intake of aspartame-containing beverages might have attenuated a modest true association between aspartame and cancer, e.g., hematopoietic cancer risk of RR < 1.24.

The NIH-AARP FFQ did not inquire about other “diet” version of foods, such as yogurt, gelatin/pudding, ice cream and frozen desserts, and hot chocolate, which currently contribute 50 mg or more aspartame per serving (40). However, aspartame use was initially limited to dry foods such as tabletop sweetener, cold breakfast cereals, or gelatin/pudding mix in 1981 then expanded to carbonated beverages in 1983 (41). Expansion of its use occurred in 1993 to include other beverages, baked goods, and confections, and finally, to all foods and beverages as a “general purpose sweetener” in 1996 (42). This limited usage history before the baseline of the NIH-AARP Study, combined with the fact that soft drinks still account for >70% of aspartame sales in the U.S. (42), lead us to consider it unlikely that a more comprehensive list of foods would have changed our results during the follow-up between 1995 and 2000.

We did not specifically query whether the “diet” beverage listed on our FFQ contained aspartame. However, we assigned aspartame because it was the artificial sweetener of choice in the beverages we studied during most of the 1980s and 1990s and therefore, that to which the NIH-AARP Study participants were primarily exposed. From 1970, when cyclamate was banned in the U.S., until 1983, saccharin was the only artificial sweetener in soft drinks (43). In 1983, aspartame mostly replaced saccharin in leading brands/varieties of soft drinks because saccharin had been linked to cancer in animal studies, for which Food and Drug Administration required a warning label on saccharin-containing products (44). The Food and Drug Administration repealed the cancer-related warning labels on saccharin in 1996 (45) and approved other artificial sweeteners for use in soft drinks, including ascesulame-K and sucralose in 1998 and neotame in 2002 (43, 44, 46).

We cannot exclude the possibility that higher aspartame consumption than that observed in this study may be associated with an elevated risk of hematopoietic or brain cancers. In the laboratory study with positive findings, animals were observed in female rats fed 20 mg of aspartame and higher (e.g., 1,200 mg for humans weighing 60 kg or 132 lb; refs. 13, 14). The reported aspartame intake in our data ranged from 0 to 3,400 mg/d with sparse numbers in the upper intake categories (>1,200 mg/d). However, we did not detect any increase in risk among those in the highest categories (>1,200 or 2,000 mg/d, which is equivalent to ~7 to 11 cans of soft drinks daily) compared with the lowest categories, and the associations were similarly null in both men and women.

The age range in our observation was up to 75 with a median of 67. According to the Surveillance, Epidemiology, and End Results statistics (1998-2000; http://seer.cancer.gov/), the median age at diagnosis was 55 for brain tumors, and the late 60s for hematopoietic cancers (67 for leukemia, 66 for non–Hodgkin lymphoma, and 70 for multiple myeloma), and between the ages of 65 and 74 for Hodgkin lymphoma of late-onset (after age 55, which accounts for ~25%). Although we will update current findings as more cases accrue, we do not particularly suspect that the results will change because there is no evidence to suggest a stronger effect of aspartame in older age and because we did not detect any differential associations in younger (<60) versus older participants in our study. The SIR comparison indicates that the rates in our cohort were generally comparable to those of the U.S. population: the slightly lower rates of overall hematopoietic cancers are not considered unusual beyond normal geographic variations (http://seer.cancer.gov/).

In conclusion, our prospective epidemiologic study suggests that aspartame consumption derived from its main source, aspartame-containing beverages, does not raise the risk of hematopoietic or brain malignancies.

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