

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

Unhee Lim,¹ Amy F. Subar,² Traci Mouw,¹ Patricia Hartge,¹ Lindsay M. Morton,¹ Rachael Stolzenberg-Solomon,¹ David Campbell,³ Albert R. Hollenbeck,⁴ and Arthur Schatzkin¹

¹Division of Cancer Epidemiology and Genetics, ²Division of Cancer Control and Population Sciences, National Cancer Institute, NIH, Department of Health and Human Services; ³Information Management Services, Inc., Rockville, Maryland; and ⁴AARP, Washington, District of Columbia

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

Received 3/14/06; revised 5/22/06; accepted 7/6/06.

Grant support: Intramural Research Program of the NIH, the National Cancer Institute. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Amy Subar, Division of Cancer Control and Population Sciences, National Cancer Institute, 6130 Executive Boulevard, EPN 4005, Rockville, MD 20852-7344. Phone: 301-594-0831; Fax: 301-435-3710. E-mail: subara@mail.nih.gov

Copyright © 2006 American Association for Cancer Research.

doi:10.1158/1055-9965.EPI-06-0203

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)

Baseline characteristics	Overall	Aspartame intake (mg/d)					
		None	>0, <100	≥100, <200	≥200, <400	≥400, <600	≥600
Cohort participants (%)	100	46	25	13	7	5	4
Aspartame (mg/d) [among users only]	111 [205]	0	47	147	267	441	986
Age at entry	62.0	62.2	62.5	61.9	61.4	60.7	59.9
Sex (% women)	40	38	44	42	41	35	34
Ethnicity (%)							
Non-Hispanic White	91	90	92	93	94	95	94
Non-Hispanic Black	4	4	4	3	3	2	3
Others	5	6	5	4	3	3	3
Education (%)							
<12 years	6	7	5	5	6	5	7
12-15	52	53	51	51	53	52	56
16+	39	37	42	41	39	40	34
Error or missing responses	3	3	3	3	3	3	3
History of diabetes (%)	9	3	9	14	19	22	26
Family history of cancer (%)	49	48	49	49	50	49	48
Alcohol (g/d)	12	14	12	11	10	11	13
Smoking (%)							
Never	36	36	37	35	33	31	29
Former	51	47	53	55	56	58	57
Current	12	15	9	9	10	10	13
Error or missing responses	2	2	2	2	2	1	2
BMI	27	26	27	28	28	29	29
≥18.5, <25 (%)	35	42	33	29	24	21	19
≥25, <30	43	42	44	46	45	45	42
≥30, <35	16	13	16	19	22	23	26
≥35	6	4	6	7	9	10	13
Physical activity (%)							
≤3-4 /mo	31	32	29	29	31	32	37
≤1-2 /wk	22	22	22	22	22	21	19
≥3-4 /wk	46	45	49	48	47	45	43
Calories (kcal)	1,835	1,919	1,692	1,734	1,844	1,855	2,044
Caffeine (mg/d)	366	393	321	336	367	364	424
Daily frequency (serving/d)							
Diet soda	0.4	—	0.2	0.6	0.9	2.2	3.5
Diet fruit drinks	0.05	—	0.03	0.1	0.2	0.1	0.2
Diet iced tea	0.1	—	0.1	0.2	0.4	0.2	0.3
Aspartame in coffee/hot tea	0.3	—	0.2	0.6	1.2	0.6	0.6

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

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

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)

Aspartame intake (mg/d)	All hematopoietic cancers									Gliomas*	
	Men and women combined			Men			Women			Men and women combined	
	Case, N = 1,888	Person-years	RR (95% CI)	Case, N = 1,318	Person-years	RR (95% CI)	Case, N = 570	Person-years	RR (95% CI)	Case, N = 315	RR (95% CI)
None	869	946,316	1.00 (Referent)	615	585,965	1.00 (Referent)	254	360,351	1.00 (Referent)	162	1.00 (Referent)
>0, <100	432	505,228	0.91 (0.81-1.03)	294	279,047	0.95 (0.83-1.10)	138	226,181	0.83 (0.67-1.02)	83	0.99 (0.75-1.29)
≥100, <200	280	274,430	1.10 (0.96-1.26)	187	158,731	1.09 (0.92-1.29)	93	115,699	1.11 (0.87-1.41)	32	0.70 (0.48-1.03)
≥200, <400	137	148,017	1.01 (0.84-1.21)	95	86,800	1.03 (0.83-1.29)	42	61,217	0.95 (0.68-1.32)	16	0.66 (0.39-1.12)
≥400, <600	104	109,262	1.05 (0.85-1.29)	76	70,059	1.07 (0.84-1.36)	28	39,204	1.02 (0.69-1.51)	22	0.73 (0.46-1.15)
≥600	66	77,357	0.98 (0.76-1.27)	51	49,960	1.06 (0.79-1.42)	15	27,398	0.80 (0.47-1.35)		
P for trend			0.56			0.42			0.87		0.05

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.

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)

Aspartame intake (mg/d)					Lymphoid malignancies* [†]	
	Hodgkin lymphoma		Multiple myeloma		Overall	
	Case, N = 57	RR (95% CI)	Case, N = 273	RR (95% CI)	Case, N = 1,279	RR (95% CI)
None	29	1.00 (—)	127	1.00 (—)	592	1.00 (—)
>0, <100	28	0.77 (0.44-1.32)	57	0.85 (0.62-1.17)	300	0.93 (0.81-1.07)
≥100, <200			48	1.39 (0.99-1.96)	177	1.01 (0.85-1.19)
≥200, <400			20	1.13 (0.70-1.83)	92	0.98 (0.78-1.22)
≥400, <600			21	1.03 (0.64-1.66)	73	1.06 (0.82-1.35)
≥600					45	0.95 (0.70-1.29)
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 lymphoma/leukemia.

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

system (ICD-O-2 histology: 9590-9989) into lymphoid and nonlymphoid (nonlymphoid leukemias) origins, and lymphoid cancers into Hodgkin lymphomas (9650-9667), non-Hodgkin lymphomas (9590-9595, 9670-9717, 9731, 9761, 9764, 9820-9830, 9850, 9940-9941, 9970), and multiple myelomas (9732). In addition, we examined certain non-Hodgkin lymphoma subtypes [small lymphocytic lymphoma (9670) and chronic lymphocytic leukemia (9823), immunoblastic lymphoma (9684), and lymphoblastic lymphoma/leukemia (9685, 9821, 9828)], and non-lymphoid leukemia (9720-9723, 9740-9741, 9800-9804, 9840-9842, 9860-9932, 9950-9962, 9980-9989) that were elevated in the aspartame-fed group in one of the animal studies (13).

Cancers of the brain and other nervous system [ICD-O-2 site: C70.0-C72.9, excluding lymphoma/leukemia of brain (ICD-O-2 histology 9590-9989)] were classified into the main subtypes of gliomas (9380-9481), meningiomas (9530-9539), and neuromas (or schwannomas, 9540-9560). Unlike tumors on other sites, the health consequences caused by benign tumors (~25% of total) of the brain and nervous system could be as serious as those caused by malignant tumors (18). However, standardized registration and reporting of benign and uncertain brain tumors have only recently begun in the U.S. (Benign Brain Tumor Cancer Registries Amendment Act, 2002; refs. 19, 20). The NIH-AARP Study acquired all brain tumor data from the eight participating registries, which included a small number of benign and uncertain cases from three registries that had collected the information with varying degrees of completeness during the relevant period (1995-2000). Because gliomas are predominantly malignant, whereas meningiomas and neuromas are mostly benign (18), we limited our analyses to malignant gliomas, leaving out the other types that were ascertained only in part, and therefore, are not adequately represented in our data.

Dietary Assessment. The self-administered baseline questionnaire included a food frequency questionnaire (FFQ) calibrated against two 24-hour recalls (15). The FFQ asked about consumption frequency of 124 food items in the past 12 months, including three potentially aspartame-containing beverages: soda ("soft drinks, soda, pop"), fruit drinks ("such as Hi-C, lemonade, and Kool-Aid"), and iced tea. Participants selected among 10 possible response categories regarding frequency ranging from "never" to "6+ times per day" and among three portion size ranges. Participants were then asked whether they usually, or more than half the time, drank the sugar-free (diet) or regular-calorie type of these beverages.

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 $\geq 10\%$. 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

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)

Non-Hodgkin lymphoma				Non-lymphoid leukemia*†	
				Case, N = 279	RR (95% CI)
Small lymphocytic lymphoma and chronic lymphocytic leukemia		Immunoblastic lymphoma and lymphoblastic lymphoma/leukemia			
Case, N = 241	RR (95% CI)	Case, N = 45	RR (95% CI)		
109	1.00 (—)	23	1.00 (—)	121	1.00 (—)
60	1.03 (0.75-1.41)	22	0.77 (0.42-1.42)	62	0.93 (0.68-1.27)
36	1.16 (0.79-1.71)			47	1.31 (0.93-1.85)
36	1.02 (0.69-1.52)			20	1.05 (0.65-1.70)
				29	1.25 (0.82-1.91)
	0.84		0.40		0.19

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 α 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 ~200 mg of aspartame daily (~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 ≥ 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 ≥ 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 $\geq 1,200$ mg/d (*n* = 12 cases) versus none, 0.85; 95% CI, 0.48-1.50; glioma RR for $\geq 1,200$ 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 ≥ 60 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 ~90% 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

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 ($r \approx 0.73$; 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 acesulfame-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 fed doses starting from 4 mg up to 5,000 mg per kg body weight. Significantly elevated lymphomas and leukemias 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% consuming $\geq 1,200$ mg/d). However, we did not detect any increase in risk estimates 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.

Acknowledgments

We are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. We thank Dr. Peter Inskip for his valuable input. We gratefully acknowledge the contributions of Leslie Carroll, Eric Berger, and Joe Barker at the Information Management Services, Inc. for programming support; Betsy Duane-Potocki-DCEG Communications Coordinator for her most helpful guidance on corresponding with research community and the media, and Tawanda Roy at the Nutritional Epidemiology Branch and Verma Walker at the NIH Library for research assistance.

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health. The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or the Department of Health. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, PA. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

References

1. Butchko HH, Stargel WW, Comer CP, et al. Aspartame: review of safety. *Regul Toxicol Pharmacol* 2002;35:S1-93.
2. Weihsrauch MR, Diehl V. Artificial sweeteners—do they bear a carcinogenic risk? *Ann Oncol* 2004;15:1460-5.
3. Olney JW, Farber NB, Spitznagel E, et al. Increasing brain tumor rates: is there a link to aspartame? *J Neuropathol Exp Neurol* 1996;55:1115-23.
4. Study E33-34 in Master File 134 on aspartame. On file at the FDA Hearing Clerk's Office 1980.
5. Shephard SE, Wakabayashi K, Nagao M. Mutagenic activity of peptides and the artificial sweetener aspartame after nitrosation. *Food Chem Toxicol* 1993; 31:323-9.
6. Ross JA. Brain tumors and artificial sweeteners? A lesson on not getting soured on epidemiology. *Med Pediatr Oncol* 1998;30:7-8.
7. Flamm WG. Increasing brain tumor rates: is there a link to aspartame?. *J Neuropathol Exp Neurol* 1997;56:105-6.
8. Koestner A. Increasing brain tumor rates: is there a link to aspartame?. *J Neuropathol Exp Neurol* 1997;56:107-9.
9. Council on Scientific Affairs. Aspartame. Review of safety issues. *JAMA* 1985;254:400-2.

10. Jeffrey AM, Williams GM. Lack of DNA-damaging activity of five non-nutritive sweeteners in the rat hepatocyte/DNA repair assay. *Food Chem Toxicol* 2000;38:335–8.
11. National Toxicology Program USDoHaHS. Toxicity studies of aspartame (CAS No. 22839–47–0) in FVB/N-TgN(v-Ha-ras)Led(Tg.AC) hemizygous mice and carcinogenicity studies of aspartame in B6.129-Trp53tm1Brd(N5) haploinsufficient mice. NTP Technical Report (NIH Publication No. 03–4459) 2003.
12. Gurney JG, Pogoda JM, Holly EA, et al. Aspartame consumption in relation to childhood brain tumor risk: results from a case-control study. *J Natl Cancer Inst* 1997;89:1072–4.
13. Soffritti M, Belpoggi F, Esposti DD, et al. Aspartame induces lymphomas and leukaemias in rats. *Eur J Oncol* 2005;10:107–16.
14. Soffritti M, Belpoggi F, Esposti DD, et al. First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environ Health Perspect* 2006;114:379–85.
15. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol* 2001;154:1119–25.
16. Michaud DS, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Registry Management* 2005;32:70–5.
17. World Health Organization Classification of Tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon (France): IARC Press; 2001.
18. Preston-Martin S, Mack WJ. Neoplasms of the nervous system. In: Schottenfeld D, Fraumeni JF, editors. *Cancer Epidemiology and prevention*. New York: Oxford University Press; 1996. p. 1231–81.
19. McCarthy BJ, Surawicz T, Bruner JM, et al. Consensus conference on brain tumor definition for registration. November 10, 2000. *Neuro-oncol* 2002;4:134–45.
20. McCarthy BJ, Kruchko C. Consensus conference on cancer registration of brain and central nervous system tumors. *Neuro-oncol* 2005;7:196–201.
21. Butchko HH, Stargel WW. Aspartame: scientific evaluation in the postmarketing period. *Regul Toxicol Pharmacol* 2001;34:221–33.
22. National Cancer Institute DSRPCSB. Surveillance, Epidemiology, and End Results (SEER) Program (<http://www.seer.cancer.gov/>) SEER*Stat Database: Incidence—SEER 9 Regs Public-Use, Nov 2004 Sub (1973–2002). <http://seer.cancer.gov/publicdata/citation.html>. 2006.
23. Lubin JH, Gail MH. On power and sample size for studying features of the relative odds of disease. *Am J Epidemiol* 1990;131:552–66.
24. Mayne ST, Risch HA, Dubrow R, et al. Carbonated soft drink consumption and risk of esophageal adenocarcinoma. *J Natl Cancer Inst* 2006;98:72–5.
25. The European Food Safety Authority. Opinion of the Scientific Panel AFC related to a new long-term carcinogenicity study on aspartame. *EFSA Journal* 2006;356:1–44.
26. Subar AF, Thompson FE, Smith AF, et al. Improving food frequency questionnaires: a qualitative approach using cognitive interviewing. *J Am Diet Assoc* 1995;95:781–8.
27. Subar AF, Ziegler RG, Thompson FE, et al. Is shorter always better? Relative importance of questionnaire length and cognitive ease on response rates and data quality for two dietary questionnaires. *Am J Epidemiol* 2001;153:404–9.
28. Thompson FE, Subar AF, Brown CC, et al. Cognitive research enhances accuracy of food frequency questionnaire reports: results of an experimental validation study. *J Am Diet Assoc* 2002;102:212–25.
29. Rimm EB, Giovannucci EL, Stampfer MJ, et al. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992;135:1114–26.
30. Colditz GA. The nurses' health study: a cohort of US women followed since 1976. *J Am Med Womens Assoc* 1995;50:40–4.
31. Kaaks R, Riboli E. Validation and calibration of dietary intake measurements in the EPIC project: methodological considerations. *European Prospective Investigation into Cancer and Nutrition*. *Int J Epidemiol* 1997;26 Suppl 1: S15–25.
32. Stram DO, Hankin JH, Wilkens LR, et al. Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. *Am J Epidemiol* 2000;151:358–70.
33. Willett WC. *Nutritional epidemiology*. 2nd ed. New York: Oxford University Press; 1998.
34. Schatzkin A, Kipnis V, Carroll RJ, et al. A comparison of a food frequency questionnaire with a 24-hour recall for use in an epidemiological cohort study: results from the biomarker-based Observing Protein and Energy Nutrition (OPEN) study. *Int J Epidemiol* 2003;32:1054–62.
35. Subar AF, Kipnis V, Troiano RP, et al. Using intake biomarkers to evaluate the extent of dietary misreporting in a large sample of adults: the OPEN study. *Am J Epidemiol* 2003;158:1–13.
36. Bingham SA, Luben R, Welch A, et al. Are imprecise methods obscuring a relation between fat and breast cancer? *Lancet* 2003;362:212–4.
37. Kristal AR, Peters U, Potter JD. Is it time to abandon the food frequency questionnaire? *Cancer Epidemiol Biomarkers Prev* 2005;14:2826–8.
38. Rosner B, Gore R. Measurement error correction in nutritional epidemiology based on individual foods, with application to the relation of diet to breast cancer. *Am J Epidemiol* 2001;154:827–35.
39. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc* 1993;93:790–6.
40. The NutraSweet Company. How much aspartame is contained in various products? Available from: <http://www.nutrasweet.com/articles/search.asp?Id=47&srch=content> 2006.
41. Food and Drug Administration. Food additives permitted for direct addition to food for human consumption: aspartame. *Fed Regist* 1983;48:31376–82.
42. Position of the American Dietetic Association: use of nutritive and nonnutritive sweeteners. *J Am Diet Assoc* 2004;104:255–75.
43. National Cancer Institute Fact Sheet. Artificial sweeteners and cancer: questions and answers. Available from: <http://www.cancer.gov/cancer-topics/factsheet/Risk/artificial-sweeteners> 2006.
44. Food and Drug Administration. Sugar substitutes: Americans opt for sweetness and lite. Available from: <http://www.cfsan.fda.gov/> 2006.
45. Food and Drug Administration. Milestones in U.S. Food and Drug Law History. Available from: <http://www.fda.gov/opa/com/backgrounders/miles.html> 2006.
46. American Beverage Association. What's in soft drinks? Available from: <http://www.ameribev.org/variety/contents.asp> 2006.