BRIEF COMMUNICATION

Aspartame Consumption in Relation to Childhood Brain Tumor Risk: Results From a Case–Control Study

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Brain cancer incidence rates in the United States have been increasing in both adults (*1*) and children (*2*). The possibility that aspartame, a widely ingested artificial sweetener, may be a cause of brain cancer in humans was suggested in a recent report by Olney et al. (*3*). From a descriptive analysis of national cancer data, they noted increased brain cancer incidence rates in the United States that coincided with the introduction of aspartame into food stuffs in the early 1980s.

As part of a population-based case–control study of environmental and nutritional risk factors for pediatric brain tumor occurrence, we collected data on aspartame consumption before the date of diagnosis for case patients (or a comparable reference date for control subjects) from the biologic mothers of study children by in-person interview. The methodology for the study has been published previously (*4*). Briefly, case patients were 19 years of age or older and were diagnosed with a primary brain tumor between 1984 and 1991 in 19 West Coast counties of the United States. Control subjects were recruited using random-digit dialing and were frequency-matched by age at diagnosis, year of birth, sex, and study site. We present data on aspartame consumption among the subset of participants from the Los Angeles and San Francisco sites where questions on aspartame consumption were added to the original questionnaire midway through the interviews. Our analysis of the child's exposure was conducted on 56 case patients and 94 control subjects who were born in 1981 or later (to correspond with the U.S. Food and Drug Administration [FDA] approval of aspartame). We also evaluated brain tumor risk in relation to mother's consumption of aspartame during pregnancy and breast-feeding for 49 case patients and 90 control subjects who were in utero in 1981 or later. We calculated odds ratios (ORs) and 95% confidence intervals and adjusted for the frequency-matched variables with the use of unconditional logistic regression. Additional adjustment for known or suspected risk factors (maternal vitamin use, cured meat consumption, passive smoke exposure, x-ray exposure, head injury, and family history of brain cancer) did not change our results.

Case children were no more likely than control children to consume foods containing aspartame, either from all sources of aspartame combined (OR = 1.1) or from diet drinks (OR = 0.9) (Table 1). There was no suggestion of a dose–response relation based on age at first consumption, number of years of consumption, or frequency of consumption. We observed no elevated brain tumor risk to the child from maternal consumption of aspartame during pregnancy nor did we find elevated risks during any trimester of pregnancy or during breast-feeding (Table 2). Additionally, we found no evidence for an aspartame–brain tumor association when the analysis was stratified by histologic subgroups (astroglial, primitive neuroectodermal, or all others). These findings are not consistent with an aspartame–brain cancer relation, although our study sample was small and the confidence intervals of our risk estimates are relatively wide. Recall bias is unlikely to have affected these results, or we would expect to see elevations in risk; however, it is conceivable that exposure misclassification that was randomly distributed between case patients and control subjects could have masked a true effect, if the true effect was weak.

We are aware of no other epidemiologic studies that have evaluated brain cancer risk from aspartame consumption. There have been numerous studies (*5-8*) related to the potential neurotoxic effects of aspartame. However, few experimental or biochemical reports related to the carcinogenicity of aspartame are in the scientific literature. Before approval of aspartame for human consumption, the FDA and an FDA-appointed public board of inquiry reviewed several studies to determine if aspartame can induce brain neoplasms in mice or rats. The mice studies were negative, but interpretation of two of the three rat studies differed initially between the FDA and its board of inquiry. These differences were resolved, and the FDA commissioner concluded that aspartame did not contribute to brain tumor formation in rats (*7-10*). A subsequent rat study also found no association between aspartame and brain tumor occurrence (*11*). Because some dietary constituents can be nitrosated in the stomach to form potentially carcinogenic *N*-nitroso compounds (*12*), Shephard et al. (*13*) evaluated the mutagenic activity of aspartame after nitrosation. They observed only a weak mutagenic effect of nitrosated aspartame at concentrations considerably higher than normal human intake levels. On the basis of the kinetics of nitrosation of mutagenic intermediates, Shephard et al. concluded that the terminal amino group of aspartame, not the amide function, was primarily nitrosated. It would be nitrosation of the amide function, not the terminal amino group, that could produce a potential brain carcinogen, based on the ability of the related nitrosoureas to induce brain tumors in laboratory animals (*14*). Thus, our review revealed little biologic or experimental evidence that aspartame is likely to act as a human brain carcinogen.

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See ''Notes'' following ''References.''

Table 1. Aspartame consumption in relation to brain tumor risk in children*

Aspartame consumption	Case patients (n = 56)		Control subjects (n = 94)		Unadjusted		Adjusted†	
	No.	%	No.	%	OR	95% CI	OR	95% CI
All sources‡	17	30	26	28	1.1	0.6-2.4	1.1	0.5-2.6
Age at first consumption, y								
<3	7	13	12	13	1.0	0.4-2.8	1.0	0.3-3.1
3-7	10	18	13	14	1.3	0.5-3.3	1.2	0.4-3.6
Years of consumption								
<2	9	16	14	15	1.1	0.4-2.8	1.2	0.4-3.3
⩾2	8	14	11	12	1.3	0.5-3.4	1.1	0.3-3.4
Frequency of consumption (times/wk)								
<1	7	13	8	9	1.5	0.5-4.5	1.6	0.5-5.2
⩾1	10	18	18	19	1.0	0.4-2.3	0.9	0.3-2.4
Diet drinks	9	16	19	20	0.8	0.3-1.8	0.9	0.3-2.4
Age at first consumption, y								
<3	4	7	8	9	0.8	0.2-2.8	0.8	0.2-3.1
3-8	5	9	10	11	0.8	0.3-2.5	1.0	0.3-3.4
Years of consumption								
<2	4	7	10	11	0.6	0.2-2.2	0.8	0.2-3.1
⩾2	5	9	8	9	1.0	0.3-3.2	0.9	0.3-3.4
Frequency of consumption (times/wk)								
<1	5	9	8	9	1.0	0.3-3.2	1.2	0.3-4.5
⩾1	4	7	11	12	0.6	0.2-1.9	0.6	0.2-2.3

*Includes only children born in 1981 or later. OR = odds ratio; CI = confidence interval.

†Questions were asked about the child's consumption of aspartame or NutraSweet, including age at first consumption, time period of consumption, and frequency of consumption, for any food, chewing gum, or diet drink.

‡The reference category is those with no reported consumption. ORs are adjusted for the study site, sex, age at diagnosis or reference date, and birth year.

Table 2. Maternal aspartame consumption during pregnancy* and breast-feeding in relation to brain tumor risk in children

Aspartame consumption	Case patients (n = 49)		Control subjects (n = 90)		Unadjusted		Adjusted†	
	No.	%	No.	%	OR	95% CI	OR	95% CI
All sources‡,§	9	18	22	24	0.7	0.3-1.6	0.7	0.3-1.7
Consumption during pregnancy, trimester	7	14	19	21	0.6	0.2-1.6	0.6	0.2-1.7
1st	6	12	18	20	0.6	0.2-1.5	0.6	0.2-1.6
2nd	7	14	18	20	0.7	0.3-1.7	0.7	0.3-1.8
3rd	6	12	18	20	0.6	0.2-1.5	0.6	0.2-1.6
Consumption during breast-feeding	5	10	14	16	0.6	0.2-1.8	0.7	0.2-2.0
Diet drinks§	5	10	11	12	0.8	0.3-2.5	0.9	0.3-2.8
Consumption during pregnancy, trimester	3	6	9	10	0.6	0.2-2.3	0.7	0.2-2.7
1st	3	6	9	10	0.6	0.2-2.3	0.7	0.2-2.7
2nd	3	6	6	7	0.9	0.2-3.9	1.1	0.3-5.1
3rd	2	4	7	8	0.5	0.1-2.6	0.6	0.1-3.2
Consumption during breast feeding	4	8	8	9	0.9	0.3-3.2	1.1	0.3-4.0

*Includes only pregnancies in 1981 and later. OR = odds ratio; CI = confidence interval.

†The reference category is those with no reported consumption. ORs are adjusted for study site, sex, age at diagnosis or reference date, and birth year.

‡Questions were asked about the mother's consumption of aspartame or NutraSweet, including trimesters of consumption, time period of consumption, and frequency of consumption, for any food, chewing gum, or diet drink during pregnancy or while breast-feeding.

§Categories are not mutually exclusive.

Because studies of children inherently limit the causal evaluation of exogenous agents that require a long time interval between exposure and a carcinogenic effect, we cannot rule out the possibility that children in our study who were exposed to aspartame will incur an increased brain tumor risk as adults. Given the almost simultaneous occurrence of the peak rise in brain tumor incidence rates with the introduction of aspartame into public food stuffs, which is inconsistent with the usual latency periods typical of solid tumor carcinogens, it appears unlikely that any carcinogenic effect of aspartame ingestion could have accounted for the recent brain tumor trends as Olney et al. contend (*3*). Although our results cannot be confidently generalized to adults, we found no evidence to support the hypothesis that consumption of aspartame is related to pediatric brain tumor occurrence.

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Notes

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