

# An International Case-Control Study of Adult Diet and Brain Tumor Risk: A Histology-Specific Analysis by Food Group

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**PURPOSE:** Existing studies of diet and adult brain tumors have been limited by small numbers in histology-specific subgroups. Dietary data from an international collaborative case-control study on adult brain tumors were used to evaluate associations between histology-specific risk and consumption of specific food groups.

**METHODS:** The study included 1548 cases diagnosed between 1984 and 1991 and 2486 control subjects from 8 study centers in 6 countries. Of the 1548 cases, 1185 were gliomas, 332 were meningiomas, and 31 were other tumor types. Dietary consumption was measured as average grams per day.

**RESULTS:** We found inverse associations between some vegetable groups and glioma risk, the strongest for yellow-orange vegetables (odds ratio [OR], 0.7, 95% confidence interval [CI], 0.5–0.9 for the 4th vs. 1st quartile of consumption,  $p$  for trend < 0.001), and the association was limited to specific glioma subtypes. There was no association with cured meat. Non-cured meat was associated with a modest increase in glioma risk (OR, 1.3; 95% CI, 1.0–1.7 for 4th quartile vs. 1st quartile,  $p$  for trend = 0.01). We also found positive associations between egg, grain, and citrus fruit consumption and glioma but not meningioma risk.

**CONCLUSIONS:** Our study suggests that selected dietary food groups may be associated with adult gliomas and its subtypes but not meningiomas.

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**KEY WORDS:** Brain Tumors, Diet, Glioma, Meningioma, N-Nitroso Compounds, Vegetables.

## INTRODUCTION

Several studies have examined the association of brain tumors in adults with cured meat and fruit/vegetable consumption with generally inconsistent results (1–12). A possible explanation for this inconsistency is the limited

ability to examine individual brain tumor histologic types as the result of relatively small sample sizes. The most common histologic types of adult brain tumor are glioma and meningioma. Glioma is the most common, with several histologic subtypes (13). Many epidemiologic studies have focused solely on risk factors for glioma without specifying more detailed subtypes. Ignoring histological subtype may result in heterogeneous case groups, masking underlying risk factor patterns and biological pathways.

Nitrite exposure has been hypothesized as an explanation for both cured meat and fruit/vegetable associations with brain tumors (1, 2, 14–16). Cured meats are the primary source of dietary *N*-nitroso compounds (NOC) and their precursors (17). Because NOC are largely formed endogenously and have been shown to be carcinogenic (18, 19), cured meats are a potential brain tumor risk factor whereas nitrosation inhibitors found in fruits and vegetables, e.g., vitamin C, may relate to reduced risk.

This work presents a pooled analysis of data from 8 study centers in 6 countries that participated in the International Collaborative Study of Adult Brain Tumors and is a companion to a similar article from the International Collaborative Study of Childhood Brain Tumors (20). We investigated cured meat, fruit/vegetable, and other dietary

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**Selected Abbreviations and Acronyms**

NOC = N-nitroso compounds  
IARC = International Agency for Research on Cancer  
OR = odds ratio  
95% CI = 95% confidence interval

associations with brain tumor risk by using the largest number of cases, to date, ever studied epidemiologically. We were able to explore whether these associations, some of which have never been studied by histology, were specific to certain histologic types and subtypes and whether there were common associations for adult and childhood brain tumors. Differences in results between the adult and childhood studies may suggest differences in importance of exposure periods; e.g., foods that appear to increase brain tumor risk in childhood but not adults may suggest that early life exposure is most critical for that particular food. Results from analyses of the effect of diet (and other factors) on risk of adult brain tumor from three participating regions have been published previously (14, 21, 22).

**METHODS**

**Selection of Cases and Controls**

The study design has been previously described in detail (23-26). Data were pooled from case-control studies of risk factors for adult brain tumors from 8 study centers in 6

countries: Heidelberg, Germany; Grenoble, France; Manitoba, Canada; Toronto, Canada; Stockholm, Sweden; Adelaide, Australia; Melbourne, Australia; and Los Angeles, California USA. Although response rates were unavailable for some study centers (Toronto, Manitoba, and Grenoble), 79% of eligible cases and 66% of first-choice eligible controls participated based on centers for which these data were available. The pooled study included 1548 cases and 2486 controls. Cases were diagnosed between 1984 and 1991 (Table 1) and included subjects between the ages of 20 and 80 years. Population-based controls were individually matched by sex and age in 5 of the study centers (Grenoble, Los Angeles, Melbourne, Stockholm, and Winnipeg) and controls were frequency-matched by sex and age in the remaining 3 centers (Adelaide, Heidelberg, and Toronto).

**Data Collection**

Data collection was coordinated by the International Agency for Research on Cancer in Lyon (IARC), France and was standardized across all 8 study centers by the use of a common protocol (25); however, each center was allowed to adapt the dietary questionnaire because of regional differences in diet. The dietary items were all part of the main questionnaire and not based on a separate food frequency questionnaire. All subjects were interviewed by trained interviewers about their usual dietary intake in the period 5 years before diagnosis by the use of detailed dietary recall methods and abstract food models or photographs of

**TABLE 1.** Number of foods per group by study center, international collaborative case-control study of adult diet and brain tumor risk

	Germany Heidelberg	Canada Toronto	Sweden Stockholm	Canada Manitoba	Australia Adelaide	France Grenoble	Australia Melbourne	USA Los Angeles
Number of Cases	194 (12%)	200 (13%)	232 (15%)	113 (7%)	182 (12%)	121 (8%)	414 (27%)	92 (6%)
Number of Controls	417 (17%)	221 (9%)	340 (13%)	326 (13%)	417 (17%)	252 (10%)	419 (17%)	94 (4%)
Diagnosis Years	1987-1989	1986-1991	1987-1990	1984-1989	1987-1990	1987-1991	1987-1991	1987-1991
<b>Food group:<sup>1</sup></b>								
All foods analyzed	40	43	49	43	59	40	59	44
All Vegetables	9	5	7	5	11	9	11	4
Cruciferous vegetables	2	3	2	3	4	1	4	2
Leafy green vegetables	2	2	3	2	2	1	2	2
Yellow/orange vegetables	1	1	1	1	1	1	1	1
Cured meat	10	8	8	8	8	8	8	6
Non-cured Meat	0	3	2	3	2	1	2	1
Fresh fish	1	1	3	1	1	1	1	1
Smoked/pickled fish	3	3	4	3	5	2	5	1
Eggs/Dairy	0	0	2	0	0	1	0	0
Cheese only	1	1	1	1	2	0	2	2
Eggs only	0	1	1	1	1	0	1	1
Grains	1	5	3	5	5	1	5	4
All fruit	3	1	4	1	7	4	7	4
Citrus fruit	2	3	2	3	2	4	2	4
Caffeine	5	3	3	3	3	3	3	3
Oil products	0	2	0	2	2	3	2	3

<sup>1</sup>Subsets of food groups did not necessarily represent the full complement of food groups; e.g., other fruit types besides citrus were included in "all fruit."

typical portions to gauge portion sizes (27). The baseline interview used at all centers did not ask about total dietary habits but rather focused on food items high in nitrate, nitrite, NOC, vitamin C, and other antioxidants (27). Each center's dietary questionnaire contained at least 40 food items (Table 1). The questionnaire used for the Los Angeles study center and a complete listing of specific foods queried by each center are available online (28). Interviews were conducted from January 1987 through April 1992.

### Data Analysis

Foods were analyzed in the following groups and subsets of groups: all vegetables, cruciferous vegetables, leafy green vegetables, yellow–orange vegetables, all meat, cured meat, noncured meat, all fish, smoked/pickled fish, fresh fish, eggs/dairy, eggs only, cheese only, grains, all fruit, and citrus fruit. Food subgroups were chosen based on food items that were on the standardized diet questionnaire. Subsets of food groups did not necessarily represent the full complement of food groups, e.g., other fruit types besides citrus were included in “all fruit.” Consumption was measured as average grams per day (g/day), with grams per serving (g/serving) for each food estimated by each study center individually. Separate series of analyses that adjusted for total dietary intake also were performed by regressing average g/day on total dietary intake and using the residual value as the exposure variable. For this purpose, total dietary intake was estimated as total intake of all foods queried. Socioeconomic status was measured by highest level of education attained and was evaluated as a potential confounder. Age-stratified analyses used 55 years (the median age among all subjects) as the cutpoint. In addition to the primary analyses that included all subjects, we also ran all final models for only those subjects who were the primary informants, i.e., excluding proxy interviews.

Quartiles of exposure were used for categorical analyses and were defined by study center based on the distributions in controls. Dose–response was evaluated by testing quartile of exposure as an ordered categorical variable. Maximum likelihood estimates of ORs and 95% confidence intervals (CIs) were derived with the use of both conditional and unconditional logistic regression (29). For conditional analyses, matched sets were defined by study center, sex, and age group for centers that frequency matched and by individual matching for all other centers. Unconditional analyses were adjusted for age, sex, and study center and were performed with the use of both all subjects and only those subjects included in conditional analyses (which excluded 503 controls [20%] in glioma analyses and 1365 controls [55%] in meningioma analyses). Generalized estimating equations were used to derive unconditional risk estimates and confidence

intervals to account for correlation within study centers (30). We did not find any major differences between the unconditional and conditional models; thus, the unconditional models using all subjects are reported here.

Both univariable and multivariable models were run. We defined “univariable” models as adjusting only for the matching factors and not other food groups and “multivariable” models as adjusting for these factors plus other food groups. Final multivariable models contained food groups that had statistically significant trends in the univariable analyses. Vitamin supplementation as a possible confounder of the cured meat effect was evaluated by comparing results with and without supplementation as a covariate. Cured meat effect modification by vitamin supplementation was evaluated by examining results from analyses stratified by vitamin supplementation and by testing the interaction between cured meat consumption and vitamin supplementation in the multivariable model. Data on vitamin supplementation were available from the collaborative database. Statistical analyses were performed using SAS, version 9.00 (SAS Institute, Inc., Cary, NC). No adjustments for multiple tests were made; all tests were performed at the 0.05 significance level.

Pathology reports for all cases of primary brain tumors were reviewed at each center and histology was coded according to the *International Classification of Diseases for Oncology* (i.e., ICD-O) classification. The primary analysis involved separate models for gliomas (n = 1185) and meningiomas (n = 332). A secondary analysis involved the glioma subtypes astrocytoma (n = 500), oligodendroglioma (n = 114), and glioblastoma (n = 542). Astrocytomas included all tumors with ICD-O codes 9400, 9420, 9410, 9411, 9401, 9421, 9424, and 9384. Oligodendrogliomas included tumors with ICD-O codes 9450 and 9451. Glioblastomas included tumors with ICD-O codes 9440, 9441, and 9442. Tumor types with fewer than 50 cases were excluded from histology-specific analyses.

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## RESULTS

Table 1 reports the number of cases and controls by each of the 8 centers and the number of foods included in each food group by center. The age of subjects ranged from 20 to 82 years with the median age ranging from 42 to 58 years across centers. There were 1185 cases of glioma; 500 of these were astrocytomas, 542 were glioblastomas, and the others were classified as “other gliomas.” There were 332 cases of meningiomas and 31 cases of histologic types other than glioma and meningioma (“other brain tumors”). There were more male than female glioblastoma cases (1.4 male:female ratio) and more female than male meningioma cases (0.4 male:female ratio). Sex ratios were close to 1.0 for astrocytomas,

other gliomas, and other brain tumors. Cases of astrocytoma and other gliomas were younger (median ages = 45 and 39 years, respectively) than cases of glioblastoma (median age = 57 years). Median ages of meningiomas and other brain tumors were 57 and 55 years, respectively. Interview by proxy was done for 314 (26%) glioma and 11 (3%) meningioma cases.

Table 2 summarizes the multivariable results for each food group for all primary brain tumors combined and for gliomas and meningiomas separately. These multivariable models simultaneously adjusted for the other food groups presented in the table. Table 3 presents multivariable results by additional subtypes of glioma (astrocytoma, oligodendroglioma, glioblastoma). Univariable and multivariable models were generally consistent, the exceptions being cured meats and fresh fish which were significant univariably but not multivariably. Supplemental models excluding proxies did not meaningfully alter any of the findings detailed below (data not shown).

Results are from multivariable models unless otherwise noted. Although we emphasize the multivariable results, univariable estimates are also presented for comparability with previous research which typically reported only univariable findings (results for all univariable models can be accessed online [28]). There was no relationship between intake of all queried foods combined and brain tumor risk; thus, all reported risk estimates are unadjusted for intake of all foods combined. Also, socioeconomic status did not alter risk estimates and thus was not included as a covariate. Reported ORs and CIs are for comparisons of fourth to first quartiles of consumption.

### Vegetables

In univariable models, both leafy green and yellow-orange, but not cruciferous, vegetables were inversely associated with glioma but not with meningioma risk. Multivariably, the inverse association between yellow-orange vegetables and glioma risk remained (OR, 0.7; 95% CI, 0.5–0.9,  $p$  for trend < 0.001; Table 2). Figure 1 depicts the relationship between yellow–orange vegetables and glioma risk by study center and shows that an inverse association was observed for all but one center (Heidelberg); ORs ranged from 0.4 to 0.9 for the other 7 centers. Heterogeneity across centers was not statistically significant. The inverse association with yellow–orange vegetables was seen for astrocytomas and glioblastomas within the glioma tumor type (Table 3). There was an inverse association between leafy green vegetables and risk of all tumors combined (OR, 0.8; 95% CI, 0.7–1.0,  $p$  for trend = 0.05; Table 2), but this appeared to be restricted to gliomas, in particular astrocytomas (OR, 0.7; 95% CI, 0.5–1.0,  $p$  for trend = 0.04; Table 3).

### Cured and Noncured Meats

The univariable OR for cured meats was 1.2 (CI, 1.0–1.5,  $p$  for trend = 0.01) for all tumors combined. Similar univariable risk estimates were observed for gliomas (OR, 1.2; 95% CI, 1.0–1.5) and meningiomas (OR, 1.3; 95% CI, 0.9–1.8), but the test for trend was significant only for gliomas ( $p$  = 0.01); however, this association was not evident multivariably, either for gliomas (Table 2) or for any other tumor subtype (Table 3). There was no evidence of confounding or effect modification by vitamin supplementation (data not shown). Noncured meat was positively associated with glioma (OR, 1.3; 95% CI, 1.0–1.7,  $p$  for trend = 0.01) but not meningioma risk (Table 2). Further analyses of other tumor subtypes suggested modest associations between non-cured meats and risk of astrocytoma, oligodendroglioma, and glioblastoma, but trend was significant only for astrocytoma (OR, 1.4; 95% CI, 1.0–1.9,  $p$  for trend = 0.04).

### Fish

There were no univariable associations for smoked/pickled fish. Fresh fish was univariably inversely associated with risk of glioma (OR, 0.7; 95% CI, 0.6–0.9,  $p$  for trend < 0.01). Multivariably, although this association did not remain for glioma risk (OR, 0.9; 95% CI, 0.7–1.1,  $p$  for trend = 0.16; Table 2), we observed a non-significant inverse trend for risk of oligodendroglioma (OR, 0.5; 95% CI, 0.2–0.9,  $p$  for trend = 0.08). Fresh fish was associated with decreased meningioma risk but only among younger (<55 years) cases (multivariable OR, 0.4; 95% CI, 0.2–0.8,  $p$  for trend = 0.01).

### Eggs/Dairy

Univariably, all egg/dairy products combined, and eggs in particular, were strongly associated with risk of glioma but not meningioma (for all eggs/dairy: OR, 1.7; 95% CI, 1.4–2.1,  $p$  for trend < 0.0001 for glioma). Multivariably, consumption of eggs remained significantly associated with risk of glioma (OR, 1.6; 95% CI, 1.3–2.0,  $p$  for trend < 0.0001; Table 2). Findings for all egg/dairy products combined and eggs separately were similar for astrocytoma and glioblastoma, with multivariable ORs ranging from 1.7 to 2.0 (Table 3). Univariably, cheese was unrelated to overall risk and risk of glioma (OR, 1.1; 95% CI, 0.9–1.5) but was significantly inversely related to risk of meningioma (OR, 0.5; 95% CI, 0.3–0.9,  $p$  for trend = 0.03).

### Grains and Fruit

Univariably, grains and fruit, citrus fruit in particular, were associated with increased risk of glioma and remained so multivariably (OR, 1.3; 95% CI, 1.1–1.7,  $p$  for trend < 0.01).

**TABLE 2.** Multivariable<sup>a</sup> ORs and 95% CIs for food groups, overall and by major tumor type, international collaborative case-control study of adult diet and brain tumor risk.

Quartile <sup>b</sup>	Controls	All tumors (n = 1548 cases)	OR (95% CI)	Glioma (n = 1185 cases)	OR (95% CI)	Meningioma (n = 332 cases)	OR (95% CI)
<b>Leafy green vegetables</b>							
1 <sup>st</sup>	651	450	1.0	347	1.0	92	1.0
2 <sup>nd</sup>	621	403	0.9 (0.7-1.1)	313	0.9 (0.7-1.1)	83	0.9 (0.6-1.4)
3 <sup>rd</sup>	701	383	0.8 (0.6-1.0)	290	0.8 (0.6-1.0)	86	0.7 (0.4-1.1)
4 <sup>th</sup>	513	312	0.8 (0.7-1.0)	235	0.8 (0.6-1.0)	71	0.9 (0.5-1.4)
<i>p</i> for trend			0.05		0.06		0.42
<b>Yellow-orange vegetables</b>							
1 <sup>st</sup>	741	520	1.0	406	1.0	103	1.0
2 <sup>nd</sup>	644	418	0.9 (0.7-1.1)	339	0.9 (0.7-1.1)	70	0.8 (0.5-1.2)
3 <sup>rd</sup>	601	334	0.8 (0.6-1.0)	244	0.8 (0.6-1.0)	86	0.9 (0.6-1.4)
4 <sup>th</sup>	500	276	0.7 (0.6-0.9)	196	0.7 (0.5-0.9)	73	0.9 (0.6-1.4)
<i>p</i> for trend			0.001		0.0006		0.64
<b>Cured meat</b>							
1 <sup>st</sup>	627	366	1.0	274	1.0	81	1.0
2 <sup>nd</sup>	625	351	0.9 (0.7-1.1)	251	0.8 (0.6-1.0)	95	1.1 (0.7-1.7)
3 <sup>rd</sup>	615	397	1.0 (0.8-1.2)	311	1.0 (0.8-1.3)	76	0.9 (0.6-1.5)
4 <sup>th</sup>	619	434	0.9 (0.7-1.1)	349	0.9 (0.7-1.2)	80	0.9 (0.5-1.5)
<i>p</i> for trend			0.49		0.76		0.57
<b>Noncured meat</b>							
1 <sup>st</sup>	774	482	1.0	361	1.0	115	1.0
2 <sup>nd</sup>	477	282	1.0 (0.8-1.2)	227	1.0 (0.8-1.2)	46	0.8 (0.5-1.1)
3 <sup>rd</sup>	396	276	1.2 (1.0-1.5)	216	1.3 (1.0-1.6)	54	1.0 (0.7-1.5)
4 <sup>th</sup>	422	314	1.2 (1.0-1.5)	270	1.3 (1.0-1.7)	36	0.6 (0.4-1.1)
<i>p</i> for trend			0.05		0.01		0.25
<b>Fresh fish</b>							
1 <sup>st</sup>	717	526	1.0	408	1.0	111	1.0
2 <sup>nd</sup>	703	403	0.9 (0.8-1.1)	284	0.9 (0.7-1.1)	104	1.2 (0.8-1.7)
3 <sup>rd</sup>	491	307	0.9 (0.7-1.1)	256	0.9 (0.7-1.1)	48	0.8 (0.5-1.5)
4 <sup>th</sup>	575	312	0.9 (0.7-1.1)	237	0.9 (0.7-1.1)	69	0.9 (0.5-1.4)
<i>p</i> for trend			0.10		0.16		0.27
<b>Eggs</b>							
1 <sup>st</sup>	500	305	1.0	248	1.0	53	1.0
2 <sup>nd</sup>	606	297	0.9 (0.7-1.1)	216	0.8 (0.6-1.0)	73	1.1 (0.7-1.6)
3 <sup>rd</sup>	359	273	1.3 (1.0-1.6)	230	1.3 (1.0-1.6)	39	1.2 (0.8-2.0)
4 <sup>th</sup>	352	358	1.6 (1.3-2.0)	318	1.6 (1.3-2.0)	32	1.3 (0.8-2.2)
<i>p</i> for trend			<0.0001		<0.0001		0.25
<b>Grains</b>							
1 <sup>st</sup>	908	508	1.0	338	1.0	156	1.0
2 <sup>nd</sup>	544	312	1.0 (0.8-1.2)	245	1.0 (0.8-1.3)	64	1.0 (0.6-1.5)
3 <sup>rd</sup>	501	330	1.1 (0.9-1.3)	268	1.1 (0.9-1.4)	58	1.0 (0.7-1.6)
4 <sup>th</sup>	533	398	1.2 (1.0-1.5)	334	1.3 (1.1-1.7)	54	0.9 (0.6-1.5)
<i>p</i> for trend			0.02		0.004		0.88
<b>Citrus fruit</b>							
1 <sup>st</sup>	645	366	1.0	281	1.0	80	1.0
2 <sup>nd</sup>	605	377	1.1 (0.9-1.3)	293	1.1 (0.9-1.4)	74	1.0 (0.7-1.6)
3 <sup>rd</sup>	645	386	1.1 (0.9-1.4)	279	1.1 (0.9-1.4)	98	1.0 (0.7-1.6)
4 <sup>th</sup>	591	419	1.4 (1.1-1.7)	332	1.4 (1.1-1.8)	80	1.1 (0.7-1.7)
<i>p</i> for trend			0.008		0.008		0.65

<sup>a</sup>Multivariable adjusted for age, sex, center and the following food groups: leafy green vegetables, yellow-orange vegetables, cured meat, noncured meat, fresh fish, dairy eggs, grains, and citrus fruit.

<sup>b</sup>Quartiles of exposure were defined by study center based on the distribution in controls.

for grains; OR, 1.4, 95% CI, 1.1-1.8, *p* for trend < 0.01 for citrus fruit; Table 2). In histology-specific analyses (Table 3), grains were related to increased risk of glioblastoma (OR, 1.4; 95% CI, 1.0-2.0, *p* for trend = 0.01) and citrus fruit was related to increased risk of astrocytoma

(OR, 1.5; 95% CI, 1.1-2.1, *p* for trend = 0.02). By sex, the grain association was apparent only among women (multivariable OR, 1.6; 95% CI, 1.1-2.4, *p* for trend = 0.03 for women; OR, 1.1; 95% CI, 0.8-1.5, *p* for trend = 0.60 for men). Citrus fruit was associated with increased risk among

younger (<55 years) cases of meningioma (OR, 2.0; 95% CI, 1.0–3.9, *p* for trend = 0.02).

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## DISCUSSION

We observed significant inverse risk associations between leafy green and yellow–orange vegetables and gliomas, especially astrocytomas, but not meningiomas. Multivariably, there were no risk associations between cured meat consumption and the major tumor types, but a slightly increased and significant glioma risk was associated with non-cured meat. We observed significant positive risk associations between egg, grain, and citrus fruit consumption and gliomas. No clear patterns of dietary associations were observed for meningiomas. Although age and sex differed by histologic subtype (e.g., glioblastoma was more common among men whereas meningioma was more common among women, and cases of astrocytoma and other gliomas were younger than cases of glioblastoma), we observed few differences in dietary risk factors by age and sex. Thus, our histology-specific associations are not likely due to varying demographic patterns among different tumor histologies.

### Comparisons With Previous Studies

Very few previously published epidemiological studies have reported on the effect of specific types of vegetables on glioma risk. A population-based case-control study from Germany observed no effect for vegetables and some evidence for reduced risk from vegetable juice (1); however, different types of vegetables were combined into a single vegetable category. Another population-based case-control study from San Francisco observed no effect for vegetables, but their vegetable categories not only combined different-colored vegetables but also included fruits (2). In China, a hospital-based case-control study observed reduced risk from vegetables but no clear dose-response (3); again, different-colored vegetables were combined and gliomas and meningiomas were analyzed together although the authors reported that results did not differ by histology. In a population-based case-control study from Nebraska that did consider different vegetable colors and that was restricted to glioma, decreased risk with significant dose-response was observed for dark yellow vegetables and there was some evidence of decreased risk for dark green vegetables (4). Most recently, an analysis of data from 3 large prospective studies in the United States found no association between glioma risk and consumption of vegetables, including yellow–orange (5). Yellow–orange vegetables are a rich source of carotenoids, which have been shown to reduce risk of cancer as the result of their antioxidant properties when consumed as part of the diet rather than through supplementation (6). It seems plausible that

decreased glioma risk may be specific to certain types of vegetables such as yellow–orange; the specificity to glioma may relate to the fact that different vegetable groups have different effects on phase I and phase II enzymes, and the action of these enzymes are affected by genetic markers (31). The inconsistent findings from studies to date suggest a need for more focused research on the potential protective effect of specific types of vegetables. Case-control dietary studies can be designed to capture more detailed histories of vegetable consumption.

Several previous studies have examined the effect of cured meat consumption on adult brain tumor risk, as the NOC hypothesis has been one of the most prominent in research of environmental risk factors for brain tumor. The first of these was a population-based case-control study of female meningioma in Los Angeles County which reported nearly a 3-fold increased risk with a significant dose-response for all cured meats combined (7). A similar study of Los Angeles County male meningioma observed increased risk that was limited to certain types of cured meat that did not remain after adjusting for head trauma (8), whereas a later study of Los Angeles County male meningioma observed an increased but nonsignificant risk for all cured meats combined (9).

In Germany, with both sexes combined, a significant positive association was observed for meningiomas and certain types of cured meats, and for gliomas and all cured meats combined (1). In a San Francisco case-control study of glioma, increased risk from all cured meats was observed among women and from bacon among men (2). In Nebraska, cured meats had no apparent association with glioma risk (4). A recently published prospective study from Maryland on cured meats and brain tumor risk reported a nonsignificant OR for gliomas of 3.7 for high cured meat consumption and a significant OR of 17.5 (95% CI, 1.1–289.5) for high cured meat plus low citrus juice consumption (10). Studies that analyzed gliomas and meningiomas combined have reported either no cured meat effect (11) or increased risk for other types of salted foods (e.g., fish, vegetables) but not for cured meats (3, 12). In summary, a cured meat association has been inconsistently observed in past research, and our findings do not support an association between cured meats and risk of either glioma or meningioma, even among subjects who took no vitamin supplements. Additional types of research studies may be needed, which can examine the possible synergistic effect of cured meats and nitrosation-inhibiting foods, i.e., it would be important to collect data on simultaneous exposure to cured meats and fruits/vegetables.

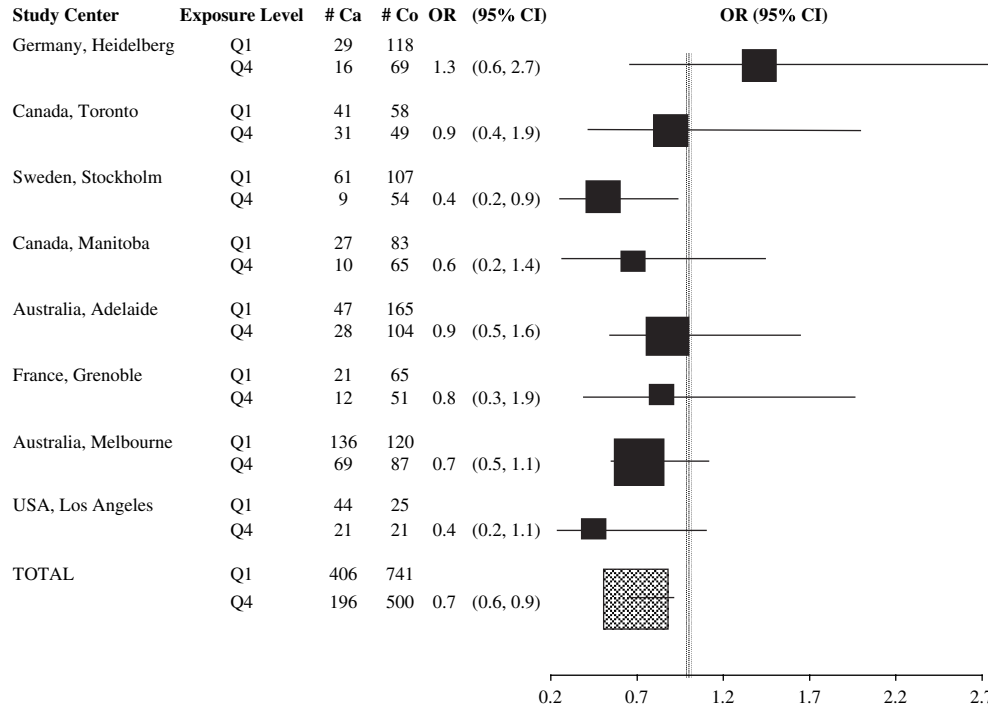
The significantly elevated glioma risk for non-cured meats in our data has not been observed by other studies that have reported on non-cured meats (2–4, 11); the fact that our noncured meat food group was somewhat of a catch-all category makes this finding difficult to interpret.

**TABLE 3.** Multivariable<sup>a</sup> OR and 95% CIs for food groups, by tumor subtype, international collaborative case-control study of adult diet and brain tumor risk

Quartile <sup>b</sup>	Controls	Astro-Cytoma (n = 500 cases)	OR (95% CI)	Oligodendro-glioma (n = 114 cases)	OR (95% CI)	Glio-Blastoma (n = 542 cases)	OR (95% CI)
<b>Cruciferous vegetables</b>							
1 <sup>st</sup>	665	151	1.0	33	1.0	127	1.0
2 <sup>nd</sup>	601	129	1.0 (0.8-1.4)	34	1.3 (0.7-2.3)	143	1.2 (0.8-1.6)
3 <sup>rd</sup>	617	116	1.0 (0.7-1.4)	27	1.0 (0.6-1.9)	129	1.2 (0.9-1.6)
4 <sup>th</sup>	603	104	0.9 (0.6-1.2)	20	0.8 (0.4-1.6)	143	1.2 (0.8-1.6)
<i>p</i> for trend			0.40		0.50		0.32
<b>Leafy green vegetables</b>							
1 <sup>st</sup>	651	161	1.0	35	1.0	142	1.0
2 <sup>nd</sup>	621	132	0.8 (0.6-1.1)	27	0.7 (0.4-1.2)	147	1.1 (0.8-1.5)
3 <sup>rd</sup>	701	121	0.8 (0.6-1.0)	38	1.1 (0.6-1.9)	125	0.9 (0.7-1.3)
4 <sup>th</sup>	513	86	0.7 (0.5-1.0)	14	0.4 (0.2-0.8)	128	1.1 (0.8-1.5)
<i>p</i> for trend			0.04		0.10		0.91
<b>Yellow-orange vegetables</b>							
1 <sup>st</sup>	741	194	1.0	38	1.0	167	1.0
2 <sup>nd</sup>	644	143	0.8 (0.6-1.1)	32	1.0 (0.6-1.8)	159	1.0 (0.7-1.3)
3 <sup>rd</sup>	601	82	0.6 (0.5-0.9)	23	1.0 (0.5-1.9)	132	0.8 (0.6-1.2)
4 <sup>th</sup>	500	81	0.7 (0.5-0.9)	21	1.0 (0.5-1.9)	84	0.6 (0.4-0.9)
<i>p</i> for trend			0.004		0.91		0.004
<b>Cured meat</b>							
1 <sup>st</sup>	627	118	1.0	20	1.0	132	1.0
2 <sup>nd</sup>	625	103	0.7 (0.5-1.0)	30	1.6 (0.8-3.0)	113	0.8 (0.6-1.1)
3 <sup>rd</sup>	615	125	0.9 (0.7-1.3)	26	1.1 (0.6-2.2)	153	1.0 (0.7-1.4)
4 <sup>th</sup>	619	154	0.9 (0.7-1.3)	38	1.5 (0.8-3.0)	144	0.8 (0.6-1.1)
<i>p</i> trend			0.78		0.43		0.33
<b>Noncured meat</b>							
1 <sup>st</sup>	774	182	1.0	44	1.0	132	1.0
2 <sup>nd</sup>	477	99	1.0 (0.8-1.4)	21	0.7 (0.4-1.3)	103	1.0 (0.7-1.4)
3 <sup>rd</sup>	396	88	1.3 (0.9-1.8)	15	0.6 (0.3-1.2)	103	1.3 (1.0-1.8)
4 <sup>th</sup>	422	117	1.4 (1.0-1.9)	28	1.4 (0.8-2.5)	115	1.2 (0.9-1.6)
<i>p</i> for trend			0.04		0.39		0.18
<b>Fresh fish</b>							
1 <sup>st</sup>	717	175	1.0	44	1.0	180	1.0
2 <sup>nd</sup>	703	129	0.8 (0.6-1.1)	29	0.6 (0.4-1.1)	117	0.9 (0.7-1.3)
3 <sup>rd</sup>	491	93	0.7 (0.5-1.0)	26	0.9 (0.5-1.6)	131	1.1 (0.8-1.5)
4 <sup>th</sup>	575	103	0.9 (0.6-1.2)	15	0.5 (0.2-0.9)	114	1.0 (0.7-1.4)
<i>p</i> for trend			0.20		0.08		0.94
<b>Eggs</b>							
1 <sup>st</sup>	500	99	1.0	42	1.0	99	1.0
2 <sup>nd</sup>	606	99	0.9 (0.7-1.3)	22	0.4 (0.2-0.8)	91	0.8 (0.6-1.1)
3 <sup>rd</sup>	359	102	1.4 (1.0-1.9)	16	0.4 (0.2-0.8)	109	1.5 (1.1-2.1)
4 <sup>th</sup>	352	139	1.7 (1.2-2.3)	26	0.7 (0.4-1.3)	143	1.8 (1.3-2.5)
<i>p</i> for trend			<0.0001		0.24		<0.0001
<b>Grains</b>							
1 <sup>st</sup>	908	121	1.0	30	1.0	182	1.0
2 <sup>nd</sup>	544	111	1.0 (0.8-1.5)	25	1.1 (0.6-2.0)	102	1.0 (0.7-1.4)
3 <sup>rd</sup>	501	131	1.2 (0.9-1.7)	24	1.1 (0.6-2.2)	104	1.0 (0.7-1.4)
4 <sup>th</sup>	533	137	1.2 (0.8-1.6)	35	1.6 (0.9-2.9)	154	1.4 (1.0-2.0)
<i>p</i> for trend			0.18		0.17		0.01
<b>Citrus fruit</b>							
1 <sup>st</sup>	645	111	1.0	26	1.0	137	1.0
2 <sup>nd</sup>	605	133	1.2 (0.9-1.6)	32	1.1 (0.6-2.0)	121	0.9 (0.7-1.3)
3 <sup>rd</sup>	645	119	1.2 (0.9-1.7)	27	1.2 (0.6-2.1)	128	1.0 (0.7-1.4)
4 <sup>th</sup>	591	137	1.5 (1.1-2.1)	29	1.5 (0.8-2.7)	156	1.3 (1.0-1.8)
<i>p</i> for trend			0.02		0.29		0.10

<sup>a</sup>Simultaneous analysis of food groups for which trends were univariably significant for at least one histological subtype. Specific food groups included differ from the childhood brain tumor analysis because different food groups were univariably significant. Models for analyses of each food group included all other foods in the table plus study center, age, and sex.

<sup>b</sup>Quartiles of exposure were defined by study center based on the distribution in controls.



**FIGURE 1.** Univariable ORs and 95% CIs relating glioma risk and fourth-quartile exposure to yellow–orange vegetables adjusted for age at diagnosis and sex, overall and by study center, international collaborative case–control study of diet and adult brain tumor risk. Sizes of boxes representing ORs are proportional to inverse variances of risk estimates. Lines through boxes depict 95% CIs.

Our finding of increased glioma risk for citrus fruit consumption contrasts with the well-known property of vitamin C as a nitrosation inhibitor. Results from previous studies that analyzed citrus fruit consumption are mixed and include decreased risk (8, 9), no effect or contradictory effects for different sources of vitamin C (4, 12), and increased risk (11). Although adjustments were made for other food groups in our multivariable analysis, it is possible that residual confounding was present; we also observed increased glioma risk from eggs and grains. Considering that citrus, eggs, grains, and cured meats are commonly consumed together (as breakfast), it would be important to extract out the individual effects of these foods to gain a clearer understanding of the possible role of nitrosation and nitrosation inhibition attributable to each, i.e., collect data not only on whether or not these foods were consumed, but on consumption alone versus together.

**Methodological Issues**

Overall our observed associations were modest (20–50% increase/decrease in risk), thus we need to carefully consider the limitations of the study and, in particular, the possible effects of bias and confounding on our results (32). For example, the lack of effect for yellow–orange vegetables in the prospective analysis noted previously may argue for

recall bias as an explanation for this observation from case-control studies like ours, i.e., it is possible that cases recalled their dietary patterns differently from controls, either because of their disease or some other factor that influenced their recall, and underreported (or controls overreported) consumption of yellow-orange vegetables, resulting in differential measurement error. Although such biased reporting is possible, there is little evidence of its existence in studies designed to specifically evaluate recall bias (33).

It is interesting to note that we observed no risk associated with consumption of caffeine, a dietary component that may be thought of as unhealthy and thus underreported by controls. Yet, relying on recall by brain tumor cases, especially glioma patients, is a unique epidemiological problem, i.e., it is possible that recall was more impaired for glioma versus meningioma cases. Because there is likely a large degree of nondifferential measurement error in the reporting of diet (34), it is also plausible that the strength of the associations we observed actually is weaker than true associations between dietary food groups and brain tumors. Further, categorization of exposure (e.g., into quartiles), as was performed in this analysis, can lead to misclassification in either direction.

Another possibility is that our findings are driven by residual confounding from unmeasured variables, such as other dietary components, that are associated in a dose-

dependent way with the food categories we analyzed, as in the breakfast-food example we noted above. Our multivariable and univariable models were largely consistent, with the exception of cured meat and fresh fish. The inclusion of the covariate total dietary intake, a method proposed to reduce correlated measurement error in dietary analyses (35), did not alter food group risk estimates. We used a surrogate for total dietary intake (total grams of questionnaire foods consumed), and it is possible that a more valid estimate may act differently on individual food group risk estimates but the pattern with an unmeasured or an incompletely measured confounder would have to mimic the histologic-specific associations we observed for our findings to be solely explained by bias.

Overall participant response rates were unavailable as some individual studies from the pooled analysis were not published previously. A general limitation for large collaborative efforts such as this is that analysis can occur long after center-specific data collection and funding have ended, making it difficult or impossible to ascertain pertinent data or information. The number of cases by study center varied, from 92 in Los Angeles to 414 in Melbourne; thus, our findings were dominated by the larger study centers and may not accurately reflect true geographical differences.

Given the differences in dietary habits across geographic regions, we could not use a single dietary questionnaire for all study centers, i.e., each center asked about region-specific foods. This resulted in nonuniform ascertainment of consumption of the food groups we analyzed that may have increased measurement error and may have increased the contribution from some study centers to the overall analysis. However, all centers based their food lists on a shortened list used in a Canadian study which was validated and shown to correlate very well with estimates based on a full diet history for dietary components key to our analysis, including nitrate, nitrite, NOC, vitamin C and other antioxidants (27). We examined whether findings for food groups differed across geographic centers and observed consistent patterns. We also observed similar findings using conditional models that maintained the individual matching factors versus unconditional models that adjusted for the matching factors.

Because this was a hypothesis-generating as well as a hypothesis-testing analysis, the overall type 1 error rate was not controlled. Therefore, results and conclusions should be interpreted keeping in mind that numerous statistical tests were done with outcomes that were clearly not independent. For example, for major tumor types, 17 food groups were analyzed for each of three subgroups (all tumors, gliomas, and meningiomas), for a total of 51 tests. If these tests were independent, we would expect two to three significant results by chance alone with a 0.05 significance level.

We observed 20 significant results, but many of these were strongly correlated; thus, more than 2 to 3 significant results could reasonably occur by chance alone. For example, because gliomas and meningiomas are subsets of all tumors combined, a false rejection of the null hypothesis for all tumors combined would also be reflected in analyses of gliomas and meningiomas. Among gliomas and meningiomas only (two disjoint groups), we observed 12 significant results when 1 to 2 would be expected; but, again, some outcomes were subsets of others (e.g., citrus fruit and all fruit).

The data in this study were collected from 1987 to 1992. Despite this lag from collection to publication, the dietary hypothesis is still relevant because no clear associations between diet and brain tumor risk have been proved or disproved. However, we acknowledge that our exposure categories for risk assessment may differ from categories (i.e., quartiles of consumption) that would result from more recent data if patterns of consumption have changed substantially during the past 2 decades. Although there are inconsistencies in glioma pathology classification by time (as well as region), we feel that the glioma subgroups we analyzed were appropriate given the years of diagnosis in our study. Additionally, a 10% pathology review of our cases did not result in substantial changes in diagnoses.

### Comparison With Childhood Companion Study

In our companion study (20), clear associations between maternal consumption of cured meats during pregnancy and increased risk of childhood brain tumors were observed, as were inverse associations between yellow–orange vegetable consumption and risk of anaplastic astrocytomas and medulloblastomas. The apparent lack of an association between cured meat consumption and adult brain tumors may be due to increased nondifferential measurement error in the adult study. Adult brain tumors likely develop during a long time period, and dietary information obtained at the time of interview may not reflect long-term patterns of intake or patterns during crucial etiologic periods.

On the other hand, the differences in findings also may be explained by biological reasons; for example, fetal brain tissue may be more sensitive to NOC exposure than adult brain tissue, as has been suggested by experimental findings (36). The histology specificity of the yellow–orange vegetable association in both childhood and adult studies is important because it argues against (i) recall bias as the sole explanation for the observed decreased risk, as discussed above; and (ii) a residual confounding effect whereby observed decreased risk with vegetable intake merely reflects a “healthy lifestyle”; if this were true, we would expect to see the effect across all tumor types and subtypes.

## CONCLUSIONS

Studies that combine all histologies may result in a case group too heterogeneous to uncover certain risk factors. Because these international collaborative studies are the largest to date of adult and childhood brain tumors and dietary risk factors, we were able to explore food group associations for individual tumor histologies, thus providing hypotheses for future, more directed research. Our findings suggest the need for dietary analysis not only by histology, but also by specific foods within a broad food group. An example of this is our analysis of vegetables, which showed that certain types of vegetables (yellow-orange and leafy green) were related to reduced risk. If the histology-specific associations we observed can be confirmed, preferably in well-designed case-control studies as noted previously, it would strengthen the foundation on which research into the etiology of adult brain tumors could be based.

We would like to acknowledge the contributions of all study participants and of the investigators and interviewers at each of the collaborating sites. We dedicate these 2 companion manuscripts to our co-author and colleague Dr. Geoffrey Howe, who died August 31, 2006, at the age of 63. Geoff was an outstanding epidemiologist who made significant, internationally recognized contributions to the fields of cancer etiology and prevention and radiation effects, a field in which he was one of the world's foremost epidemiologists.

Geoff worked on the IARC-coordinated international collaborative case-control brain tumor studies since 1984, when investigators from countries around the world met in Lyon, France, on several occasions to plan the studies. In many aspects of these efforts, such as designing a consensus questionnaire for each study that could be used in all participating countries, Geoff's broad experience in case-control studies of brain tumors, radiation, and diet proved a huge asset. An additional asset was his impressive recall on day 3 of each meeting, when we often seemed to have come full circle in our discussion of an issue; Geoff was able to tell us what the group had decided after exhaustive discussion of that issue on day 1 or 2. Perhaps he developed this striking aural recall because he had gone blind from diabetes some years before.

During the last few years, Geoff worked closely with those of us who did the analysis of the dietary data and in numerous conference calls guided us (M.B.T., J.M.P., S.P.-M.) in our discussion of issues related to statistical approaches and presentation of results. His collaboration in the preparation of these manuscripts was invaluable.

Geoff, we thank you for your guidance, inspiration, and wit. It was indeed a pleasure working with you and getting to know you personally. You were an outstanding colleague and a warm friend to many of us. We feel honored to have known you.

Susan Preston-Martin, Mary Beth Terry, Janice M. Pogoda, and all the collaborators on the IARC-coordinated case-control studies of primary brain tumors in adults and children.

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