

Diet and risk of adult glioma in eastern Nebraska, United States

Honglei Chen^{1,2}, Mary H. Ward^{2,*}, Katherine L. Tucker¹, Barry I. Graubard², Rodney D. McComb³, Nancy A. Potischman⁴, Dennis D. Weisenburger³ & Ellen F. Heineman²

¹Tufts University, Human Nutrition Research Center on Aging, Boston, MA, USA; ²National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, MD, USA; ³University of Nebraska Medical Center, Department of Pathology and Microbiology, Omaha, NE, USA; ⁴National Cancer Institute, Division of Cancer Control and Population Sciences, Bethesda, MD, USA

Received 23 August 2001; accepted in revised form 1 April 2002

Key words: carotenoids, diet, glioma, N-nitroso compounds, phytochemicals.

Abstract

Objective: To investigate potential associations between diet and adult glioma.

Methods: We conducted a population-based case-control study of adult glioma in eastern Nebraska. Nutrient and food group intakes were estimated for 236 glioma cases and 449 controls using information obtained from a food-frequency questionnaire.

Results: After adjusting for potential confounders, inverse associations with risk of adult glioma were observed for intakes of dark yellow vegetables (highest quartile versus lowest: OR = 0.6, $p_{\text{trend}} = 0.03$) and beans (OR = 0.4, $p_{\text{trend}} = 0.0003$), but no associations were seen for dietary sources of preformed nitrosamines or high-nitrate vegetables. Our nutrient analysis revealed significant inverse associations between risk of adult glioma and dietary intake of pro-vitamin A carotenoids (highest quartile versus lowest: OR = 0.5, $p_{\text{trend}} = 0.005$), α -carotene (OR = 0.5, $p_{\text{trend}} = 0.01$), β -carotene (OR = 0.5, $p_{\text{trend}} = 0.01$), dietary fiber (OR = 0.6, $p_{\text{trend}} = 0.048$) and fiber from beans (OR = 0.5, $p_{\text{trend}} = 0.0002$). We observed no significant associations with risk of adult glioma for intakes of other nutrients or compounds including nitrate, nitrite, vitamin C, vitamin E, saturated fat, cholesterol, dietary fiber from grain products, or fiber from fruit and vegetables.

Conclusion: Our study does not support the N-nitroso compound hypothesis, but suggests potential roles for carotenoids and possibly other phytochemicals in reducing risk of adult glioma.

Introduction

Brain cancer is among the most lethal cancers in the United States. According to the cancer Surveillance, Epidemiology, and End Result (SEER) program, the overall 5-year relative survival rate for this cancer was only about 28.3% during 1989–1996 [1]. In the US the rates of brain cancer are highest among white men, followed by white women and black men and women [1]. After a small peak in the first decade of life the risk of this cancer increases appreciably after age 50 and reaches its

peak at 70–80 years of age [1, 2]. Among adults more than 90% of malignant tumors in the brain are gliomas, which are composed of a variety of cancers arising from the neuroglial cells, typically including astrocytoma, oligodendroglioma, and ependymoma [2, 3].

Compared with more common cancers, such as breast cancer and colorectal cancer, adult glioma has received less attention until recently. High-dose ionizing radiation is the only established risk factor, but this uncommon exposure may account for only a small fraction of adult glioma in the general population [3]. Other suspected risk factors include familial predisposition and certain occupational exposures such as organic solvents and electromagnetic fields [3].

The associations between dietary intakes and adult glioma are not well understood. However, N-nitroso

* Address correspondence to: Dr Mary H. Ward, PhD, Occupational Epidemiology Branch, National Cancer Institute, 6120 Executive Blvd, EPS-8104, MSC-7420, Bethesda, Maryland, 20892-7420, USA. E-mail: wardm@exchange.nih.gov

compounds (NOC) have been thought to be important. There are two kinds of NOC: nitrosamines and nitrosamides. Animal studies have revealed that nitrosamides, particularly alkylnitrosoureas, are strong nervous system carcinogens [4]. Human exposure to NOC comes from both exogenously and endogenously formed compounds. The volatile nitrosamines are more readily analyzed than nonvolatile nitrosamines and nitrosamides and therefore have been measured in many foods, beverages, and other consumer products. Although many foods probably contain both types of compounds, volatile nitrosamines have been used in epidemiological studies as an estimate of exposure to preformed NOC. Some studies have found that greater intakes of volatile nitrosamines [5, 6] or one or more of their dietary sources, such as processed meats, beer, cheese, salted fish, and salted vegetables [5–10] were related to increased risk of adult glioma. However, others failed to observe such associations [11–18].

Limited data suggest associations of other dietary factors with adult glioma. Greater intakes of antioxidants (vitamin C and E), fruit and vegetables, and the use of vitamin supplements have been related to lower risk of adult glioma [8–10, 16, 17]; whereas greater intakes of total energy [18] and protein [16] have been associated with higher risk. However, the epidemiological evidence for these dietary factors is not consistent. Higher serum cholesterol concentration was found to be associated with greater risk of adult glioma in a few studies [19–21], but not in others [22–24]. To further investigate associations between diet and adult glioma we examined data from a population-based case-control study in eastern Nebraska.

Materials and methods

Study population

The current study was part of the Nebraska Health Study II, which was designed to investigate the potential roles of occupational and dietary risk factors in adult glioma, esophageal adenocarcinoma, and stomach cancer in 66 counties of eastern Nebraska. A detailed description of the study design has been described elsewhere [25]. Histologically confirmed incident primary adult glioma cases were identified from the Nebraska Cancer Registry or 11 participating hospitals in Lincoln and Omaha, covering more than 94% of all adult glioma cases in the study population between 1 July, 1988 and 30 June, 1993. All participants were white male or female residents of these 66 counties, aged 21 years or older.

Controls for this study were randomly selected from the control group of a previous population-based case-control study of non-Hodgkin's lymphoma, Hodgkin's disease, multiple lymphoma, and chronic lymphocytic leukemia conducted in 1986–1987 in the same base population [26]. In the previous study the controls were selected from the base population by 3:1 frequency matching by race, gender, vital status, and 5-year age groups to the overall case distribution. A two-stage random-digit dialing method was used for living cases under age 65; whereas Medicare records were used for random selection of older controls. For deceased cases the controls were selected from the Nebraska state mortality files with additional matching for year of death [26, 27]. In the current study the controls were frequency matched to the overall distribution of the adult glioma, esophageal, and stomach cancer cases by age, gender, and vital status to ensure adequate overlap of these variables for individual cancer analysis. Because of inadequate numbers of younger controls for the adult glioma study, 23 additional controls identified by random-digit dialing ($n = 3$) or from death certificates ($n = 20$) were interviewed.

Interviews

Telephone interviews with cases and controls or their proxies were performed during 1992–1994 by trained interviewers. Of the 298 cases still eligible after review by a neuropathologist (R.M.), 267 (90%) were successfully interviewed. Sixteen were determined to be ineligible (based on interview information) due to residence outside of Nebraska during the study period. Of the 251 eligible interviewed cases, approximately 87% were astrocytic tumors (including 58% glioblastoma multiforme), 8% were oligodendroglial tumors, 3% ependymal tumors, 1% mixed gliomas, and 2% other gliomas. A total of 606 eligible controls were identified and we interviewed 498 controls or their proxies (82%). Taking into account the response rate of controls in the previous study (87%), the response rate for re-interviewed controls was 71% in the current study. Reasons for non-response included refusals from participants or their physicians (20 cases and 56 controls), no identifiable next of kin (no cases and 11 controls), failure to contact (eight cases and 23 controls), and other reasons (three cases and 18 controls). The interviews followed a standardized questionnaire modified from the one used in the former lymphoma study, with additional questions related to suspected brain cancer risk factors. Participants were asked to recall exposures prior to 1985. The interviews were conducted with the next-of-kin or another proxy respondent for 76% of cases

and 60% of controls. The majority of proxy respondents were either the patients' spouses (cases: 64%; controls: 49%) or other first-degree relatives (cases: 32%; controls: 44%). Self-respondent controls were intentionally over-sampled to increase the power of subgroup analyses among self-respondents.

Dietary assessment and food group definition

A 48-item food-frequency questionnaire was used to assess participants' dietary habits. This questionnaire was modified from the short Health Habits and History Questionnaire [28]. Modifications were made to collect more information on foods containing preformed NOC, nitrate, or nitrite. A few foods that contributed to salt, fat, and calorie intake were dropped to reduce the burden on brain cancer cases. These foods were also excluded from the analyses that included brain cancer cases and controls. The correlation coefficients for these nutrient intakes among controls calculated with or without the dropped foods were usually 0.95 or above. The reliability of reported dietary intakes was evaluated for foods that were asked about in both interviews. The Spearman correlation coefficients ranged from 0.32 to 0.49 (mean 0.41) and they were similar between self-respondents and proxy respondents.

Detail on frequency of consumption of each food was requested, and age- and gender-specific portion sizes were used to calculate nutrient intakes. Dietary intakes of nitrate and nitrite were determined from published literature [29–34]. Mean nutrient intakes and their standard deviations (SD) by case-control status are presented in Appendix 1. In addition to food intakes details of the use of vitamin supplements and intake of alcoholic drinks, including beer, wine, and liquor, were also requested.

Before data analysis the food groups were defined as the following: dairy products (2%, 1%, or skim milk or beverages made with milk; whole milk or beverages made with whole milk; and cheeses and cheese spread, not including cottage cheese); processed meats (bacon; sausage, including breakfast sausage; processed or smoked ham, bought from store; meat that was cured or smoked at home; sandwich meats, such as bologna or salami; and hot dogs); red meats (beef, such as steak or roasts; beef stew or pot pie; hamburgers, cheeseburgers, or meatloaf; fresh ham, ham roast, pork chops, or pork roast; liver, including chicken liver); poultry (chicken or turkey); fish (fish, either fresh, frozen, or canned, such as trout or tuna fish); gravy made from meat juice; total vegetables including: dark green vegetables (broccoli and spinach); dark yellow vegetables (carrots or mixed vegetables with carrot; sweet potatoes or yams); high-

nitrate vegetables (radishes; lettuce or green salad; coleslaw, cabbage or sauerkraut; celery; rhubarb; beets; spinach); tomatoes or tomato juice; green beans; and onions; beans, dried peas, and chili; citrus fruit and juices (oranges, tangerines, or grapefruit; and orange juice or grapefruit juice); white bread including sandwiches, bagels, and crackers; dark bread including whole wheat, rye, and pumpernickel; and breakfast cereals (highly fortified cereal, cooked cereal, and other cold cereal). The median and inter-quartile range (25–75%) for the individual food groups are presented in Appendix 2.

Volatile nitrosamines such as N-nitrosopyrrolidine can be formed when cured meats, particularly bacon, are fried. Moreover, meats cooked at high temperatures and for a long duration may contain carcinogens such as heterocyclic amines [35] and a preference for well-done beef was associated with higher risk of stomach cancer in this study population [25]. Therefore, we also assessed whether beef doneness (defined as rare/medium rare, medium, medium well/well done) or cooking methods for beef, pork, and poultry (baked/roasted/boiled, fried/broiled, grilled/barbecued) were associated with risk of adult glioma.

Statistical analysis

Dietary variables were categorized before data analysis according to their distribution among controls. Most food intakes were grouped into quartile categories and energy intake was adjusted as a covariate in the logistic regression models. Intakes of white and dark breads were categorized into tertiles because of the limited distribution of intakes. Nutrient intakes were categorized into quartiles with adjustment for energy intake, using the residual method [36]. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated by unconditional logistic regression. All significance tests were two-sided ($\alpha = 0.05$).

We tested for linear trends by including the median of each quartile as a continuous variable in the model and testing for the significance of the slope. Analyses of the food group and nutrients separately by gender and respondent type gave similar results; therefore the overall results are presented. Age, age squared, gender, respondent type, family history, education level, and farming experience were adjusted in all analyses. Family history was defined as having any first-degree relatives ever diagnosed with a tumor of the central nervous system. Education was categorized into two levels: completed high school and less than a high school degree. Farming experience was defined as having ever lived or worked on a farm. Because education level and

farming experience showed different associations with adult glioma by gender, we also included their interaction terms with gender in all models.

Results

Cases and controls with unknown or missing intakes for 20% or more of the food items were excluded from analyses [25]. This left 236 (94%) adult glioma cases (132 men and 104 women) and 449 (90%) controls (258 men and 191 women) in the dietary analysis.

Table 1 shows characteristics of the study sample by gender and case-control status. For both men and women the cases tended to be younger than controls as a result of the frequency matching by age across all case groups including gastrointestinal cancer patients. Women reported lower energy intake than men, but there was no difference between cases and controls. For both genders the cases had more proxy respondents than controls. A higher proportion of cases completed 12 or more years of schooling than controls, and the difference was more pronounced among women. For both men and women higher proportions of cases reported family histories of any cancer or cancer of the central nervous system than controls. More male cases reported farming experience than male controls, whereas the opposite was true for female cases and controls. About 27% of male cases and controls had used vitamin supplements prior to 1985, whereas supplement use was reported by 42% of female cases and 51% of female controls.

Table 2 describes associations between food group intakes and risk of adult glioma. Greater intake of dark yellow vegetables was significantly associated with lower

risk of adult glioma ($p_{\text{trend}}=0.03$). An even stronger inverse association was found for intake of beans that included beans, dried peas, and chili (ORs for increasing intake quartiles: 1.0, 1.2, 0.6, and 0.4, $p_{\text{trend}}=0.0003$). Higher weekly consumptions of fish, total vegetables, high-nitrate vegetables, and dark bread were nonsignificantly associated with lower risk of adult glioma, whereas consumption of dairy products was nonsignificantly associated with higher risk. No other food group intakes, including individual processed meats (bacon, sausage, sandwich meats, ham, and hotdogs) or beer, were associated with risk of adult glioma (data not shown). We also found no associations between beef doneness or meat cooking method and risk of adult glioma (data not shown).

Associations of nutrient intake residual quartiles with risk of adult glioma are shown in Table 3. Total energy intake was not related to risk. Compared with the lowest quartiles, the highest intake quartiles of total pro-vitamin A carotenoids, α -carotene, and β -carotene were each associated with an approximately 50% lower risk and significant inverse trends were observed for all these nutrients. Risk of adult glioma was also found to be 40% lower for the highest quartile of dietary fiber intake *versus* the lowest. Further analysis showed that only the association with fiber from beans showed a significant inverse trend. The only nutrient that tended to be positively associated with the risk was retinol, with a marginal significant trend ($p_{\text{trend}}=0.053$). No association with adult glioma was found for dietary intake of nitrate, nitrite, vitamin C, vitamin E, saturated fat, or cholesterol; neither did we find a significant interaction between dietary intakes of vitamin C and nitrite (data not shown). Moreover, the results were not meaning-

Table 1. Characteristics of the study sample

	Men		Women	
	Control (n = 258)	Case (n = 132)	Control (n = 191)	Case (n = 104)
Age (years) ^a	60.2 ± 16.9	52.8 ± 15.4	58.9 ± 18.4	54.0 ± 15.7
Energy intake (MJ)	8.1 ± 3.0	8.7 ± 2.8	5.7 ± 2.3	5.3 ± 2.1
Self-respondent (%) ^b	38.8	26.5	47.1	21.2
Years of education (%)				
<12	32.1	21.7	30.6	10.7
12	27.9	31.8	31.1	38.8
>12	40.0	46.5	38.3	50.5
Family history of cancers (%)				
Any cancer	48.3	52.9	51.4	59.8
Cancer in central nervous system	3.4	5.8	1.7	6.2
Ever lived or worked on a farm (%)	62.4	67.9	67.0	52.9
Ever took vitamin supplements (%)	27.4	27.6	51.4	41.7

^a Means and standard deviations are presented for continuous variables.

^b Proportions are presented for categorical variables.

Table 2. Odds ratios^a and 95% confidence intervals for adult glioma according to food or food group intake quartiles

Foods or food groups	Q1		Q2		Q3		Q4		<i>P</i> _{trend}
	No. cases/ controls	OR	No. cases/ controls	OR (95% CI)	No. cases/ controls	OR (95% CI)	No. cases/ controls	OR (95% CI)	
Dairy products	54/111	1.0	55/114	1.4 (0.8–2.4)	59/116	1.4 (0.8–2.5)	68/108	1.8 (1.0–3.3)	0.06
Processed meat	48/115	1.0	72/112	1.7 (1.0–2.8)	60/113	1.2 (0.7–2.0)	56/109	1.1 (0.6–2.1)	0.9
Red meat	57/113	1.0	52/114	0.8 (0.5–1.3)	67/111	0.9 (0.5–1.6)	60/111	0.9 (0.5–1.6)	0.9
Poultry	75/117	1.0	82/177	0.7 (0.4–1.1)	50/97	0.7 (0.4–1.2)	29/58	0.8 (0.4–1.5)	0.4
Fish	89/138	1.0	59/103	0.8 (0.5–1.3)	65/144	0.7 (0.4–1.1)	23/64	0.6 (0.3–1.2)	0.09
Gravy	54/128	1.0	55/91	1.8 (1.1–3.1)	83/136	1.6 (0.9–2.6)	44/94	1.7 (0.9–3.1)	0.4
All vegetables	75/112	1.0	54/113	0.7 (0.4–1.2)	60/112	0.8 (0.5–1.3)	47/112	0.5 (0.3–1.0)	0.06
Dark green vegetables	67/117	1.0	58/127	0.8 (0.5–1.3)	59/97	0.9 (0.5–1.6)	52/108	0.7 (0.4–1.2)	0.3
Dark yellow vegetables	67/113	1.0	69/117	0.9 (0.5–1.4)	53/106	0.7 (0.4–1.2)	47/113	0.6 (0.3–1.0)	0.03
Tomatoes	62/114	1.0	65/111	1.3 (0.8–2.2)	54/119	1.0 (0.6–1.7)	55/105	1.2 (0.7–2.0)	0.8
High-nitrate vegetables	56/113	1.0	79/112	1.2 (0.7–2.0)	54/112	1.0 (0.6–1.7)	47/112	0.7 (0.4–1.3)	0.1
Citrus fruit	62/113	1.0	65/117	1.1 (0.6–1.8)	50/104	0.8 (0.5–1.3)	59/115	1.0 (0.6–1.7)	0.7
Beans	61/100	1.0	101/148	1.2 (0.7–2.0)	54/130	0.6 (0.3–1.0)	20/71	0.4 (0.2–0.8)	0.0003
Dark bread ^b	98/159	1.0	67/139	0.6 (0.4–1.0)	71/151	0.7 (0.4–1.0)			0.1
White bread ^b	81/149	1.0	75/162	0.9 (0.6–1.4)	80/138	1.4 (0.8–2.2)			0.3
Breakfast cereals	60/114	1.0	56/100	1.2 (0.7–2.1)	51/104	1.1 (0.6–1.9)	69/131	1.5 (0.9–2.5)	0.2

^a Compared with the lowest intake quartile or tertile, adjusting for age, age squared, gender, total energy intake, respondent type, education level, family history, and farming experience.

^b Intake tertile, rather than quartile, was used.

Table 3. Odds ratios^a and 95% confidence intervals for adult glioma according to nutrient intake residual quartiles

Nutrient	Q1		Q2		Q3		Q4		<i>P</i> _{trend}
	No. cases ^b	OR	No. cases	OR (95% CI)	No. cases	OR (95% CI)	No. cases	OR (95% CI)	
Total energy	68	1.0	42	0.7 (0.4–1.2)	59	0.9 (0.5–1.6)	67	1.0 (0.6–1.9)	0.6
Pro-vitamin A carotenoids	85	1.0	49	0.7 (0.4–1.1)	58	0.6 (0.4–1.0)	44	0.5 (0.3–0.8)	0.005
α -carotene	83	1.0	49	0.6 (0.4–1.0)	53	0.6 (0.4–1.0)	51	0.5 (0.3–0.8)	0.01
β -carotene	83	1.0	49	0.8 (0.5–1.3)	58	0.7 (0.4–1.1)	46	0.5 (0.3–0.9)	0.01
β -cryptoxanthin	64	1.0	56	0.9 (0.5–1.5)	62	0.9 (0.6–1.5)	54	0.7 (0.4–1.3)	0.3
Lycopene	52	1.0	72	1.2 (0.7–2.0)	56	0.8 (0.5–1.5)	56	0.9 (0.5–1.6)	0.6
Lutein	53	1.0	74	1.7 (1.0–2.9)	54	1.1 (0.6–1.8)	55	1.2 (0.7–2.1)	0.9
Retinol	54	1.0	65	1.1 (0.6–1.8)	54	1.2 (0.7–2.1)	63	1.6 (1.0–2.8)	0.053
Folate	52	1.0	80	1.4 (0.8–2.3)	51	0.9 (0.5–1.6)	53	0.9 (0.5–1.5)	0.3
Vitamin C	56	1.0	67	1.2 (0.7–2.1)	61	1.3 (0.8–2.3)	52	0.9 (0.5–1.5)	0.7
Vitamin E	66	1.0	57	1.0 (0.6–1.6)	51	0.8 (0.5–1.3)	62	0.8 (0.5–1.4)	0.4
Dietary fiber	83	1.0	54	0.6 (0.4–1.0)	52	0.7 (0.4–1.2)	47	0.6 (0.3–0.9)	0.048
From beans	58	1.0	103	1.7 (1.0–2.7)	39	0.5 (0.3–0.9)	36	0.5 (0.3–0.9)	0.0002
From grain	64	1.0	47	0.7 (0.4–1.2)	68	1.3 (0.8–2.1)	57	0.9 (0.6–1.6)	0.7
From fruit/vegetable	66	1.0	75	1.0 (0.6–1.7)	40	0.7 (0.4–1.1)	55	0.9 (0.5–1.5)	0.4
Dietary fat	56	1.0	53	0.9 (0.5–1.6)	73	1.3 (0.8–2.1)	54	1.0 (0.6–1.7)	0.8
Saturated fat	49	1.0	63	1.1 (0.7–1.9)	69	1.4 (0.8–2.4)	55	1.3 (0.7–2.2)	0.4
Cholesterol	52	1.0	77	1.6 (1.0–2.7)	52	1.0 (0.6–1.8)	55	1.5 (0.8–2.5)	0.5
Protein	70	1.0	56	0.7 (0.4–1.3)	48	0.6 (0.3–1.0)	62	0.7 (0.4–1.1)	0.07
Nitrate	59	1.0	81	1.2 (0.7–1.9)	43	0.7 (0.4–1.2)	53	0.7 (0.4–1.2)	0.1
Nitrite	66	1.0	66	1.0 (0.6–1.7)	57	0.9 (0.5–1.5)	47	0.8 (0.5–1.3)	0.3

^a Compared with the lowest nutrient residual quartile, adjusting for age, age-squared, gender, respondent type, education level, family history, and farming experience.

^b The number of controls ranged from 110 to 119 for each nutrient quartiles.

Table 4. Odds ratios^a (OR) and 95% confidence intervals (CI) for the risk of adult glioma according to vitamin supplement uses

Supplement	Controls	Cases	OR (95% CI)
Nonuser	266	148	1.0
Multivitamin	136	68	0.8 (0.5–1.3)
Vitamin C	60	34	1.0 (0.6–1.7)
Vitamin E	26	15	0.8 (0.4–1.9)
Vitamin A	11	7	0.8 (0.2–2.7)

^a Compared with vitamin supplement nonusers (OR = 1), adjusting for age, age-squared, gender, respondent type, education level, family history, and farming experience.

fully different by respondent type. For example, the age- and gender-adjusted ORs for increasing quartiles of total pro-vitamin A intake for increasing quartiles of total pro-vitamin A intake compared with the lowest quartile were 0.6, 0.6, and 0.5 among self-respondents and 0.8, 0.8, and 0.5 among proxy respondents. The ORs for quartiles 1–4 of bean intake were 1.0 (reference), 1.0, 0.4, and 0.3 for self-respondents and 1.0, 1.2, 0.7, and 0.4 for proxy respondents. Finally, no vitamin supplement uses were associated with risk of adult glioma (Table 4). Further adjustment of the nutrient intakes from foods for the respective dietary vitamin intake did not change the results (data not shown).

Discussion

In this study we did not observe greater risk of adult glioma with higher intake of foods containing NOC, including processed meats and beer. Moreover, we found no significant associations between adult glioma and dietary intake of nitrate or nitrite, the precursors of endogenous NOC synthesis. However, we did observe a significantly lower risk of adult glioma with higher intake of dark yellow vegetables, beans, and certain nutrients from these foods.

Thirteen case-control studies [5–12, 14–18, 37] and one cohort study [13] have examined the association between diet and adult glioma. The findings have been inconsistent with respect to the NOC hypothesis. Among them, six case-control studies [5–10] reported elevated risks for higher intakes of nitrosamines or one or more kinds of processed meats or beer. However, the results were inconsistent within or across individual studies.

In the current study the major dietary sources of N-nitrosamines, including individual types of processed meats and beer, were not associated with risk of adult glioma. There are several potential explanations for the lack of association between dietary nitrosamines and

adult glioma in epidemiological studies. First, animal experiments support nitrosamides, but not nitrosamines, as carcinogens to the central nervous system. Because our assessment of NOC intake was based on dietary intakes of preformed nitrosamines, dietary nitrosamide intake may have been misclassified. Second, other major environmental exposures to nitrosamines and nitrosamides include specific occupational exposures, cigarette smoking, and beer drinking. However, the relationship between adult glioma and occupational exposure to NOC is not clear and epidemiological studies do not support an association with either cigarette smoking or alcohol use [3]. Third, an appropriate measurement of relevant NOC exposure is difficult because of the complexity of its exogenous exposure and endogenous synthesis. Misclassification of NOC exposure may be difficult to avoid in epidemiological studies. Finally, prenatal exposure to NOC may be important in adult glioma pathogenesis because animal data suggest that prenatal or transplacental exposure to nitrosamides confers much more risk than exposure in adult life [3].

Vitamin C, vitamin E, and other polyphenols from fruit and vegetables are antioxidants and inhibitors of endogenous NOC syntheses, and therefore may be protective against adult glioma. The epidemiological evidence for inverse associations between glioma risk and dietary intakes of vitamin C, vitamin E, their supplements, and fruit and vegetables has not been consistent [5, 6, 8–13, 16–18], with the majority of studies finding no associations. However, Lee *et al.* [9] reported that men with high intake of nitrite and low intake of vitamin C had a higher risk of adult glioma compared with low nitrite and high vitamin C intake (OR = 2.1, 95% CI 1.1–3.8), suggesting an interaction between dietary vitamin C and nitrite. We did not observe any association with risk of adult glioma for vitamin C, vitamin E, their supplements, or citrus fruit and juices, or any elevated risks for high dietary nitrite or nitrate intake in this study. Further, there was no elevated risk among those with higher dietary nitrite and lower vitamin C intakes compared with low nitrite and high vitamin C intakes.

Although carotenoids are hypothesized to protect against a variety of cancers, their association with risk of adult glioma has rarely been evaluated in epidemiological studies. Giles *et al.* [6] did not find any association with intakes of yellow vegetables or β -carotene among men, but they observed that the highest tertiles of both intakes were each associated with a nonsignificant 30% lower risk among women. Hu *et al.* [10] also reported a nonsignificant inverse association between β -carotene

intake and risk of brain cancer (ORs for intake quartiles, 1.0, 0.45, 0.51, 0.38, $p_{\text{trend}} = 0.11$) in a Chinese population. In the current study we found that higher intakes of dark yellow vegetables, pro-vitamin A carotenoids, α -carotene, and β -carotene were all significantly associated with lower risk for adult glioma.

Lee *et al.* [9] found that male glioma patients reported significantly lower intake of green beans and legumes than did male controls. In this study we observed a strong inverse association between dietary intake of dried beans or fiber from beans and risk of adult glioma. Dietary fiber has been reported to be associated with lower risk for several epithelial cancers; however, there has been no evidence to suggest its role in adult glioma. Moreover, we did not find lower risk with greater intakes of dietary fiber from other sources such as fruit and vegetables or grain products. Therefore, the inverse association observed in this study could be potentially attributed to other components found in beans. Such candidates include phytochemicals which have been hypothesized to play important roles in cancer prevention in several ways [38], including through their weak estrogenic and antiestrogenic properties, protease inhibition activities, antioxidant effects, cell apoptosis induction activities, and potential influences on signal transduction. Our data also indicate that greater intake of dark bread tends to be associated with lower risk, though the association may not be linear. This, too, is in line with a potential protective role of phytochemicals [39]. However, because this study was not designed specifically to examine potential roles of beans or phytochemicals in adult glioma, and because there have been few studies in this area, our results must be interpreted with caution and further investigations are needed.

Our study had several limitations. Like most studies of adult brain cancer, data collection in this study involved the use of next-of-kin respondents. We performed subgroup analysis by respondent type and found that the results were not meaningfully different. Adult glioma cases or their proxies might recall diets systematically differently from controls because of their symptoms, the effects of their treatment, or their perceptions of the causes of brain cancer. However, cases and controls reported similar energy intake, arguing against a systematic bias due to cancer symptoms or treatment. Moreover, the associations between diet and adult glioma, unlike some other cancers, have not been well publicized and the results for glioma are not the same as those seen for the other cancers in this study [40]. The error inherent in recalling past dietary habits would be expected to cause some exposure misclassification, although recalled diet has been found

to be more closely associated with past diet than with current diet [41]. Finally, we did not adjust for multiple comparisons in the analyses; thus the significance levels of individual comparisons must be interpreted with caution.

Together, our results point to protective roles for carotenoids and possibly phytochemicals in vegetables, beans, and grain products, but do not support a role for dietary sources of N-nitroso compounds in the etiology of adult glioma. Hypotheses other than N-nitroso compounds should be considered in further studies of diet and adult glioma.

Acknowledgements

The authors acknowledge Ms Shannon Merkle and Ms Jane Curtin of IMS for programming support. We thank Mrs Carol Russell, Mr Bob Saal of Westat, Inc., and Ms Casey Boudreau of Survey Research Associates for their contribution to data collection and management; Ms Monica Seeland and the Nebraska Cancer Registry for providing data; interviewers and support staff for their diligent work, and the many physicians, hospital staff, and study participants who cooperated in this study. We also thank Dr Robert M. Russell for his valuable comments.

Appendix 1. Mean (\pm SD) of nutrient intakes across case-control status

Nutrient	Controls (n = 449)	Glioma cases (n = 236)
Total energy (MJ)	7.1 \pm 2.9	7.2 \pm 3.0
Pro-vitamin A carotenoids (μ g)	2865 \pm 1908	2539 \pm 1768
α -Carotene (μ g)	409 \pm 362	341 \pm 294
β -Carotene (μ g)	2340 \pm 1492	2106 \pm 1422
β -Cryptoxanthin (μ g)	71 \pm 50	69 \pm 52
Lycopene (μ g)	1070 \pm 811	1057 \pm 817
Lutein (μ g)	1462 \pm 1097	1419 \pm 1080
Retinol (μ g-RE)	941 \pm 599	924 \pm 547
Folate (μ g)	318 \pm 143	317 \pm 155
Vitamin C (mg)	123 \pm 66	118 \pm 68
Vitamin E (mg α -TE)	6.7 \pm 3.4	6.8 \pm 3.6
Dietary fiber (g)	10.4 \pm 4.3	9.7 \pm 4.3
From beans (g)	1.8 \pm 1.6	1.3 \pm 1.3
From fruit and vegetables (g)	4.9 \pm 2.4	4.7 \pm 2.6
From grain (g)	3.6 \pm 2.0	3.6 \pm 2.0
Dietary fat (g)	76 \pm 37	76 \pm 35
Saturated fat (g)	32 \pm 16	32 \pm 16
Cholesterol (g)	409 \pm 222	404 \pm 207
Protein (g)	83 \pm 33	85 \pm 38
Nitrate (mg)	133 \pm 78	125 \pm 80
Nitrite (mg)	1.1 \pm 0.6	1.1 \pm 0.5

Appendix 2. Median and interquartile range (25–75%) of consumption frequency (times/week) of foods or food groups

Foods or food groups	Controls (n = 449)		Glioma cases (n = 236)	
	Median	Interquartile range	Median	Interquartile range
Dairy	14	9.2–21	15	10–22
Processed meats	5.3	2.9–8.5	5.3	3.4–8.5
Red meat	5.3	3.7–7.2	5.5	3.9–7.4
Poultry	1.0	0.9–2.0	1.0	0.7–2.0
Fish	0.7	0.2–1.0	0.47	0.2–1.0
Gravy	2.0	0.5–3.0	2.0	0.9–3.0
All vegetables	13	8.8–18	12	7.9–17
Dark green vegetables	0.5	0.0–1.0	0.41	0.0–1.0
Dark yellow vegetables	1.1	0.6–2.2	1.0	0.5–2.0
Tomatoes	1.6	0.7–2.8	1.4	0.6–2.8
High-nitrate vegetables	5.0	2.9–8.2	4.7	3.0–7.5
Citrus fruits	6.0	2.0–8.1	5.0	2.0–8.0
Beans	0.5	0.2–1.0	0.5	0.2–0.9
Dark bread	2.0	0.0–7.0	1.0	0.0–7.0
White bread	7.0	2.0–14	7.0	2.4–14
Breakfast cereals	4.0	1.7–7.0	4.0	1.7–7.0

References

- Ries L, Eisner M, Kosary C, et al., eds (2000) *SEER Cancer Statistics Review, 1973–1997*. Bethesda, MD: National Cancer Institute.
- Thomas T, Inskip P (1996) Brain and other nervous system. In: Harras A, Edwards B, Blot W, Ries LG, eds. *Cancer Rates and Risks*. Bethesda, MD: National Cancer Institute, NIH, pp. 114–119.
- Inskip PD, Linet MS, Heineman EF (1995) Etiology of brain tumors in adults. *Epidemiol Rev* **17**: 382–414.
- Hathcock J, ed. (1982) *Nutritional Toxicology*, Vol. 1. New York: Academic Press, pp. 327–381.
- Boeing H, Schlehofer B, Blettner M, Wahrendorf J (1993) Dietary carcinogens and the risk for glioma and meningioma in Germany. *Int J Cancer* **53**: 561–565.
- Giles GG, McNeil JJ, Donnan G, et al. (1994) Dietary factors and the risk of glioma in adults: results of a case-control study in Melbourne, Australia. *Int J Cancer* **59**: 357–362.
- Ahlbom A, Navier IL, Norell S, Olin R, Spannare B (1986) Nonoccupational risk indicators for astrocytomas in adults. *Am J Epidemiol* **124**: 334–337.
- Blowers L, Preston-Martin S, Mack WJ (1997) Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). *Cancer Causes Control* **8**: 5–12.
- Lee M, Wrensch M, Miike R (1997) Dietary and tobacco risk factors for adult onset glioma in the San Francisco Bay Area (California, USA). *Cancer Causes Control* **8**: 13–24.
- Hu J, La Vecchia C, Negri E, et al. (1999) Diet and brain cancer in adults: a case-control study in northeast China. *Int J Cancer* **81**: 20–23.
- Burch JD, Craib KJ, Choi BC, et al. (1987) An exploratory case-control study of brain tumors in adults. *J Natl Cancer Inst* **78**: 601–609.
- Preston-Martin S, Mack W, Henderson BE (1989) Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res* **49**: 6137–6143.
- Mills PK, Preston-Martin S, Annegers JF, et al. (1989) Risk factors for tumors of the brain and cranial meninges in Seventh-Day Adventists. *Neuroepidemiology* **8**: 266–275.
- Hochberg F, Toniolo P, Cole P, Salzman M (1990) Nonoccupational risk indicators of glioblastoma in adults. *J Neurooncol* **8**: 55–60.
- Ryan P, Lee MW, North B, McMichael AJ (1992) Risk factors for tumors of the brain and meninges: results from the Adelaide Adult Brain Tumor Study. *Int J Cancer* **51**: 20–27.
- Kaplan S, Novikov I, Modan B (1997) Nutritional factors in the etiology of brain tumors: potential role of nitrosamines, fat, and cholesterol. *Am J Epidemiol* **146**: 832–841.
- Hu J, Johnson KC, Mao Y, et al. (1998) Risk factors for glioma in adults: a case-control study in northeast China. *Cancer Detect Prev* **22**: 100–108.
- Schwartzbaum JA, Fisher JL, Goodman J, Octaviano D, Cornwell DG (1999) Hypotheses concerning roles of dietary energy, cured meat, and serum tocopherols in adult glioma development. *Neuroepidemiology* **18**: 156–166.
- Davey-Smith G, Shipley M (1989) Plasma cholesterol concentration and primary brain tumors. *BMJ* **299**: 26–27.
- Neugut AI, Fink DJ, Radin D (1989) Serum cholesterol and primary brain tumours: a case-control study. *Int J Epidemiol* **18**: 798–801.
- Nygren C, von Holst H, Mansson JE, Fredman P (1997) Increased levels of cholesterol esters in glioma tissue and surrounding areas of human brain. *Br J Neurosurg* **11**: 216–220.
- Davey-Smith G, Neaton JD, Ben-Shlomo Y, Shipley M, Wentworth D (1992) Serum cholesterol concentration and primary malignant brain tumors: a prospective study. *Am J Epidemiol* **135**: 259–265.
- Knekt P, Reunanen A, Teppo L (1991) Serum cholesterol concentration and risk of primary brain tumours. *BMJ* **302**: 90.
- Herrinton LJ, Friedman GD (1995) Serum cholesterol concentration and risk of brain cancer. *BMJ* **310**: 367–368.
- Ward MH, Sinha R, Heineman EF, et al. (1997) Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference. *Int J Cancer* **71**: 14–19.
- Zahm SH, Weisenburger DD, Babbitt PA, et al. (1990) A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* **1**: 349–356.

27. Ward M, Zahm S, Weisenburger D, *et al.* (1994) Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). *Cancer Causes Control* **5**: 422–432.
28. Block G, Hartman AM, Naughton D (1990) A reduced dietary questionnaire: development and validation. *Epidemiology* **1**: 58–64.
29. Panalaks T, Iyengar J, Donaldson B, Miles W, Sen N (1974) Further survey of cured meat products for volatile N-nitrosamine. *J Assoc Official Anal Chem* **57**: 806–812.
30. Chilvers C, Inskip H, Caygill C, *et al.* (1984) A survey of dietary nitrate in well-water users. *Int J Epidemiol* **13**: 324–331.
31. Panalaks T, Iyengar JR, Sen NP (1973) Nitrate, nitrite, and dimethylnitrosamine in cured meat products. *J Assoc Official Anal Chem* **56**: 621–625.
32. Howe GR, Harrison L, Jain M (1986) A short diet history for assessing dietary exposure to N-nitrosamines in epidemiologic studies. *Am J Epidemiol* **124**: 595–602.
33. White JW, Jr (1975) Relative significance of dietary sources of nitrate and nitrite. *J Agric Food Chem* **23**: 886–891.
34. National Academy of Sciences (1981) *The Health Effects of Nitrate, Nitrite and N-nitroso Compounds*. Washington, DC: National Academy Press.
35. Sinha R, Rothman N, Salmon CP, *et al.* (1998) Heterocyclic amine content in beef cooked by different methods to varying degrees of doneness and gravy made from meat drippings. *Food Chem Toxicol* **36**: 279–287.
36. Willett WC, Howe GR, Kushi LH (1997) Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* **65**: 1220S–1228S; discussion 1229S–1231S.
37. Preston-Martin S, Mack W (1991) Gliomas and meningiomas in men in Los Angeles County: investigation of exposures to N-nitroso compounds. *IARC Sci Publ* **105**: 197–203.
38. Messina MJ (1999) Legumes and soybeans: overview of their nutritional profiles and health effects. *Am J Clin Nutr* **70**: 439S–450S.
39. Slavin JL, Martini MC, Jacobs DR, Jr, Marquart L (1999) Plausible mechanisms for the protectiveness of whole grains. *Am J Clin Nutr* **70**: 459S–463S.
40. Chen H, Ward M, Graubard B, *et al.* (2002) Nutrient intakes and adenocarcinoma of the esophagus and distal stomach. *Nutr Cancer* (In press).
41. Friedenreich CM, Slimani N, Riboli E (1992) Measurement of past diet: review of previous and proposed methods. *Epidemiol Rev* **14**: 177–196.