Research Article

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Dietary Components Related to *N*-Nitroso Compound Formation: A Prospective Study of Adult Glioma

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Abstract

Background: *N*-nitroso compounds (NOC) are found in processed meat and are formed endogenously from intake of nitrite and nitrate. Endogenous NOC formation is antagonized by nitrosation inhibitors in fruit and vegetables (e.g., vitamin C) and promoted by heme in red meat. It has been hypothesized that a diet resulting in high exposure to NOCs increases adult glioma risk.

Methods: Using proportional hazards models, we tested this hypothesis among 545,770 participants in the prospective NIH-AARP Diet and Health Study, which assessed dietary intake at baseline (1995–1996) with a comprehensive food frequency questionnaire, and at ages 12 to 13 years with an abbreviated food frequency questionnaire.

Results: During follow-up through 2003, 585 participants were diagnosed with glioma. We found no significant trends in glioma risk for consumption of processed or red meat, nitrate, or vitamin C or E. We found significant positive trends for nitrite intake from plant sources (hazard ratio for quintile 5 versus quintile 1, 1.59; 95% confidence interval, 1.20–2.10; *P* for trend = 0.028) and, unexpectedly, for fruit and vegetable intake (hazard ratio, 1.42; 95% confidence interval, 1.08–1.86; *P* for trend = 0.0081). Examination of interactions between dietary intakes (e.g., nitrite and vitamin C) and a limited analysis of diet at ages 12 to 13 years provided no support for the NOC hypothesis.

Conclusions: Our results suggest that consumption of processed or red meat, nitrite, or nitrate does not increase adult glioma risk, and that consumption of fruit and vegetables, vitamin C, or vitamin E does not reduce risk.

Impact: Our results, in agreement with the only previous prospective analysis, cast doubt on the NOC hypothesis in relation to dietary intake and adult glioma risk. *Cancer Epidemiol Biomarkers Prev; 19(7); 1709–22.*

Introduction

N-nitroso compounds (NOC) include two chemical classes, nitrosamines and nitrosamides, which are formed by the reaction of amines and amides, respectively, with nitrosating agents derived from nitrite (1-4). Nitrosamides, which are direct alkylating agents that do not require metabolic activation (2, 5), are potent neurocarcinogens in animal models, especially through transplacental or perinatal exposure (1-4, 6, 7). Consequently, it has been hypothesized that a diet resulting in high exposure to NOCs increases glioma risk (2-4, 6, 7).

Diet accounts for the majority of exogenous exposure to NOCs for most individuals (8). Nitrosamines are found in nitrite-preserved foods, most notably processed meat, although the presence of the chemically more unstable nitrosamides is less likely (2, 5, 9-12). Endogenous NOC formation is estimated to account for 45% to 75% of total exposure to NOCs (8). Processed meat is a major dietary source of nitrite, amines, and amides—all of the precursors necessary for endogenous formation of NOCs in the stomach (2, 9-12). Furthermore, NOCs may be formed endogenously after consumption of nitrate, which can be reduced to nitrite, primarily by bacteria in the oral cavity (2, 4, 12). In addition to processed meat, the main sources of dietary nitrite are grain products and some vegetables (12). The main source of dietary nitrate is vegetables, especially leafy vegetables (12). Dietary nitrosation inhibitors, including vitamins C and E and polyphenols, abundant in fruit and vegetables, inhibit endogenous NOC formation (2-4, 6, 13). Heme in red meat stimulates endogenous NOC formation in the gastrointestinal tract (14-16). It is plausible that NOCs formed

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endogenously in the stomach or intestines are absorbed into the bloodstream and reach the brain (2).

Case-control studies provide suggestive evidence for a positive association between maternal intake of processed meat during pregnancy and risk of childhood brain tumors and, less consistently, for an inverse association between maternal intake of fruit, vegetables, dietary vitamins C and E, and vitamin supplements and childhood brain tumor risk (2, 17). Limitations of these studies included incomplete ascertainment of dietary intakes and the potential for recall and selection bias (2, 18).

Case-control studies examining the relationship between dietary factors and adult glioma have suffered from additional methodologic limitations, including a high proportion of proxy respondents among cases, failure to control for energy intake, and small number of cases (19, 20). Thus, it is not surprising that epidemiologic studies of the relationship between dietary factors related to the NOC hypothesis and adult glioma risk have been inconsistent (3, 4, 6). A meta-analysis of nine case-control studies suggested a positive association between processed meat intake and adult glioma risk; however, methodologic limitations of the individual studies prompted the authors to temper their conclusions and call for further studies (19). A recently published, large international case-control study observed no association between processed meat intake and adult glioma risk (21).

The hypothesis that a diet resulting in high exposure to NOCs increases adult glioma risk was prospectively examined in combined data from the Health Professionals Follow-up Study, Nurses' Health Study I, and Nurses' Health Study II (20, 22). No support for this hypothesis was found.

The current investigation further examined this hypothesis in the NIH-AARP Diet and Health Study. Specifically, we tested the hypotheses that high dietary intake of processed meat, red meat, nitrite, and nitrate increase glioma risk; that high intake of fruit and vegetables, vitamin C, and vitamin E reduce glioma risk; and that the association between nitrite and nitrate intake and glioma risk is modified by intake of nitrosation inhibitors (e.g., vitamin C or E) and nitrosation promoters (e.g., red meat).

Furthermore, because animal experiments (1, 2) and several epidemiologic studies (23-25) suggest that early life exposures may influence risk of adult glioma, we used data on diet at ages 12 to 13 years collected by the NIH-AARP Diet and Health Study to test the hypothesis that a diet resulting in high exposure to NOCs during adolescence increases adult glioma risk.

Materials and Methods

Study population and cohort follow-up

The NIH-AARP Diet and Health Study has been described previously (26). The study was initiated in 1995 to 1996 with the mailing of a self-administered questionnaire on demographic characteristics, dietary intake, and health-related behaviors to 3.5 million members of AARP (formerly the American Association of Retired Persons) ages 50 to 71 years who resided in one of six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two U.S. metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

Of 566,402 participants who satisfactorily completed the questionnaire, we excluded individuals who had questionnaires completed by proxy respondents (n = 15,760) or had prevalent brain cancer at baseline (n = 23). After these exclusions, we further excluded persons who reported extreme values for energy intake (n = 4,849). The final analytic cohort consisted of 545,770 participants (322,347 men and 223,423 women).

Cohort follow-up methods for vital status and cancer diagnoses have been described previously (27, 28). Glioma cases were identified through probabilistic linkage with state cancer registries. We defined gliomas as malignant brain neoplasms [International Classification of Diseases for Oncology, third edition (ICD-O-3) topography codes C710-C719 and behavior code 3] with a microscopically confirmed ICD-O-3 histology code between 9380 and 9460.

Dietary and covariate assessment

At baseline in 1995 to 1996, dietary intake was assessed with a self-administered 124-item food frequency questionnaire (FFQ). Participants were asked to report their usual frequency of intake and portion size over the previous 12 months using 10 predefined frequency categories and 3 categories of portion size. The food items, portion sizes, and nutrient database were constructed using methods developed by Subar et al. (29) with national dietary data from the U.S. Department of Agriculture's 1994 to 1996 Continuing Survey of Food Intakes by Individuals (CSFII; ref. 30). The CSFII nutrient database was supplemented by linking food codes from this database with similar foods in the nutrient database of the Nutrition Data Systems for Research from the University of Minnesota, which has nutrient values not available from the CSFII Nutrient Database (31).

The primary food groups used in our analysis included processed meat (red and white meat sources of bacon, sausage, luncheon meats, cold cuts, ham, and hot dogs), red meat (all types of beef, pork, and lamb, including bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage, and steak), fruit and vegetables, fruit, whole fruit, fruit juices, and vegetables. We also used 13 fruit and vegetable botanical subgroups created based on botanical taxonomy (32). Food groups were defined using the MyPyramid Equivalents Database (MPED), an updated version of the Pyramid Servings Database, which provides food groups that align with the 2005 Dietary Guidelines for Americans (33) and

U.S. Department of Agriculture's 2005 MyPyramid Food Guidance System (34). The MPED database uses a recipe file to disaggregate food mixtures into their component ingredients and assign them to food groups. The MPED units for food intake are ounce equivalents and cup equivalents per day.

The nitrite and nitrate contents of over 3,000 food items were determined by conducting a review of the literature focusing on U.S. and Canadian foods and calculating means of the published values weighted by the number of samples analyzed (35, 36). If values from U.S. or Canadian foods were unavailable, we used values from other Western countries. The nitrite and nitrate values for foods constituting a FFQ line item were combined by weighting the food-specific values by sex-specific intake amounts based on national dietary data from the 1994 to 1996 CSFII (29). In addition to calculating daily dietary intakes of nitrite and nitrate (both in milligrams) from all foods, we calculated nitrite and nitrate intake from plant, animal, and processed meat sources separately. Furthermore, we also estimated intake of nitrite and nitrate from processed meat sources from a database of the nitrite and nitrate content of processed meats created from measurements done on processed meats purchased in 2004 (37, 38). Finally, because ingestion of water with a nitrate content at or above the maximum contaminant level of 10 mg/L as nitrate-nitrogen may be the primary contributor to nitrate intake, we conducted an alternate analysis in which we excluded cohort members whose baseline residence was located in census tracts where an estimated 50% or more of the inhabitants had a drinking water source nitrate content at or above this level (39).

Daily dietary intakes of vitamins C (mg) and E (international units, IU) were estimated from the nutrient database. The FFQ also queried about frequency and type of vitamin supplements used over the last 12 months.

The FFQ was validated using two nonconsecutive 24-hour recalls in a subset of the cohort (40). For fruit and vegetables, energy-adjusted correlation coefficients between the FFQ and the 24-hour recalls were 0.72 and 0.61 in men and women, respectively. The baseline questionnaire also collected information about demographic characteristics, medical history, height and weight, lifestyle factors, and census tract of residence.

To assess the relationship between dietary intake at ages 12 to 13 years and adult glioma risk, we used a second questionnaire that collected information in late 1996 to 1997 on additional factors that were not queried in the baseline questionnaire, including height and weight at age 18 years, physical activity at ages 15 to 18 years, and an abbreviated FFQ about frequency of intake of 37 selected food items at ages 12 to 13 years. Of the 545,770 participants in our analytic cohort, 322,178 responded satisfactorily to the second questionnaire. For this subset of participants, we performed a limited analysis of pertinent dietary intakes (processed meat, nitrite plus nitrate from processed meat sources, red meat, and vitamin C) at ages 12 to 13 years and adult glioma risk. The abbreviated FFQ queried about intake of the main processed meats (bacon or sausage; hot dogs or frankfurters; and cold cuts or luncheon meats, such as ham, bologna, salami, corned beef, or pastrami), as well as major sources of vitamin C (e.g., oranges, grapefruit, tangerines; orange juice or grapefruit juice; fresh tomatoes, including in salads; and broccoli). Although assessment of red meat intake was incomplete (e.g., pork, roast ham or ham steak, and liver were not queried), we estimated red meat intake by summing intake of the processed meats; ground beef in hamburgers, cheeseburgers, meatloaf, meatballs, casseroles; and roast beef or steak (including in sandwiches), recognizing the limitations of this variable. Sex- and age-specific portion sizes for calculation of intake of processed and red meat (grams), nitrite and nitrate from processed meat sources, and dietary vitamin C were estimated from national dietary data from the 1965 to 1966 Household Food Consumption Survey (41), the survey done closest to the calendar time when cohort members were ages 12 to 13 years. We estimated energy intake at ages 12 to 13 years based on the abbreviated FFQ, recognizing the limitations of this estimate.

Statistical analysis

Hazard ratios (HR) and two-sided 95% confidence intervals (95% CI) for glioma in relation to intake of various dietary factors were estimated using Cox proportional hazards models using the PROC PHREG procedure (SAS version 9.1.3, SAS Institute). Follow-up time for each participant extended from the date of return of the baseline questionnaire in 1995 to 1996 to the date of first brain cancer diagnosis, date of death, date moved out of a cancer registry ascertainment area, or date of last follow-up on December 31, 2003, whichever occurred first. Follow-up time was used as the underlying time metric. We tested for and found no meaningful departures from the proportional hazards assumption. For all comparisons, P values were based on two-sided tests, with $P < 0.05$ indicating statistical significance.

We categorized dietary intakes into quintiles, with the exception of the fruit and vegetable botanical groups and individual food items, which we categorized into tertiles. We categorized intake of vitamins C and E from supplements according to a priori cut points. We conducted tests for linear trend across categories (quintiles, tertiles, or a priori cut points) by assigning participants the median intake for their categories and modeling this median value as a continuous variable, with the P value determined by a Wald test.

We adjusted consumption of foods, nitrite, nitrate, and vitamins C and E from dietary sources for energy intake using the nutrient density method (42), in which intake is normalized according to energy intake (per 1,000 kcal) and energy intake is included as a covariate in the model. To model intake of vitamins C and E from supplements, we used a standard multivariate model that included

Table 1. Baseline characteristics of study participants by quintile of processed meat intake and fruit and vegetable intake per 1,000 kcal

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
No. of participants	109,154	109,154	109,154	109,154	109,154
Processed meat intake					
Median processed meat intake*	0.08	0.17	0.28	0.43	0.78
Men					
No. of men	45,652	56,642	65,942	73,821	80,290
Age† (y)	62.8	62.4	62.2	62.2	62.3
Non-Hispanic white (%)	88.8	92.2	93.1	93.7	93.7
College graduate/postgraduate (%)	51.6	47.7	45.6	42.9	39.2
Height† (m)	1.78	1.78	1.78	1.79	1.78
Previous cancer diagnosis‡ (%)	8.4	8.4	8.6	8.3	8.3
Energy intake† (kcal/d)	1,945	1,962	1,997	2,071	2,049
Nitrite intake† §	0.67	0.61	0.61	0.64	0.74
Nitrate intake† §	55.5	46.3	43.3	41.2	40.3
Red meat intake* †	0.54	0.90	1.13	1.34	1.65
Fruit and vegetable intake† ‖	2.7	2.3	2.1	2.0	1.9
Women					
No. of women	63,502	52,512	43,212	35,333	28,864
Age† (y)	62.1	61.8	61.8	61.9	62.2
Non-Hispanic white (%)	88.0	90.7	90.5	90.0	89.6
College graduate/postgraduate (%)	35.7	30.8	27.6	25.9	23.8
Height† (m)	1.63	1.63	1.63	1.63	1.63
Previous cancer diagnosis‡ (%)	10.6	10.6	10.4	10.8	11.0
Energy intake† (kcal/d)	1,539	1,536	1,574	1,633	1,623
Nitrite intake† §	0.71	0.65	0.65	0.67	0.76
Nitrate intake† §	72.0	60.1	55.7	54.2	53.2
Red meat intake* †	0.51	0.84	1.04	1.19	1.42
Fruit and vegetable intake† ‖	3.1	2.6	2.5	2.4	2.3
Fruit and vegetable intake					
Median fruit and vegetable intake‖	1.1	1.7	2.2	2.8	3.8
Men					
No. of men	78,929	72,612	65,498	57,683	47,625
Age† (y)	61.7	62.2	62.5	62.7	62.9
Non-Hispanic white (%)	93.4	93.9	93.3	92.2	89.0
College graduate/postgraduate (%)	35.8	44.9	48.0	48.9	48.9
Height† (m)	1.78	1.79	1.78	1.78	1.78
Previous cancer diagnosis‡ (%)	8.2	8.4	8.6	8.6	8.1
Energy intake† (kcal/d)	2,278	2,063	1,954	1,856	1,769
Nitrite intake† §	0.58	0.63	0.67	0.70	0.76
Nitrate intake† §	24.0	35.9	44.8	55.1	77.1
Processed meat intake* †	0.48	0.46	0.43	0.39	0.30
Red meat intake* †	1.38	1.33	1.20	1.03	0.77
Women					
No. of women	30,225	36,542	43,656	51,471	61,529
Age† (y)	61.2	61.7	62.0	62.2	62.3
Non-Hispanic white (%)	90.8	91.7	91.4	90.0	86.4
College graduate/postgraduate (%)	21.3	26.8	30.5	32.4	33.5
Height† (m)	1.63	1.63	1.63	1.63	1.63
Previous cancer diagnosis‡ (%)	10.4	10.8	10.4	11.1	10.5
Energy intake† (kcal/d)	1,712	1,651	1,599	1,537	1,462
Nitrite intake† §	0.58	0.63	0.66	0.70	0.78

(*Continued on the following page*)

Table 1. Baseline characteristics of study participants by quintile of processed meat intake and fruit and vegetable intake per 1,000 kcal (Cont'd)

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Nitrate intake[†] [§]	26.6	39.8	50.2	63.4	95.4
Processed meat intake* [†]	0.37	0.35	0.32	0.29	0.22
Red meat intake* [†]	1.13	1.10	1.01	0.88	0.66

*MPED ounce equivalents/1,000 kcal/d.
[†]Mean values.
[‡]Other than nonmelanoma skin cancer per cancer registry diagnosis or other than basal cell carcinoma per participant self-report.
[§]mg/1,000 kcal/d.
[‖]MPED cup equivalents/1,000 kcal/d.

daily intake of the supplemental micronutrient (not per 1,000 kcal), energy intake, and other covariates. In all models, we adjusted for energy intake (continuous), age (continuous), race (non-Hispanic white, non-Hispanic black, other), education (<high school, high school graduate, post–high school other than college, some college, college graduate, and postgraduate), height (eight prespecified categories), and history of cancer at baseline (yes, no). We adjusted for height because it recently has been shown to be a risk factor for glioma (23, 43), including in this cohort (23). Including cigarette smoking in the models did not appreciably change our findings; we did not present results adjusted for smoking for this reason and because smoking has not been shown to be related to glioma risk (44, 45). We included missing values for adjustment covariates as dummy variables in the models. In selected analyses, we mutually adjusted dietary intake variables for each other.

In the analyses of dietary factors at ages 12 to 13 years, we normalized dietary intakes according to energy intake at ages 12 to 13 and adjusted for the covariates included in the models for adult diet as well as for energy intake at ages 12 to 13 years, body mass index (BMI) at age 18 years (kg/m^2; five prespecified categories), and physical activity at ages 15 to 18 years (quintiles of metabolic equivalent-hours per week, based on reported frequency of engagement in light and moderate/vigorous activities). We adjusted for the latter two covariates because they have been shown to be associated with increased glioma risk in this cohort (23). Including BMI at age 18 years and physical activity at ages 15 to 18 years in the models for adult diet did not change the HR estimates; these results are not presented. We did not adjust for baseline (1995–1996) BMI or adult physical activity (during the past 10 years) because these variables were not related to glioma risk (23).

To test for effect modification (statistical interaction) between two dietary intakes (e.g., nitrite and dietary vitamin C), we categorized each intake as low versus high (using the median intake as the cut point) and included in a multivariate model the two intakes and a cross-product term, with the *P* value for interaction determined by a Wald test for the cross-product term. In a similar manner, we also tested for statistical interactions between dietary intakes (as quintiles) and sex. In the tables, sex-specific results are shown for dietary intakes with significant sex interactions.

To test the robustness of our findings, we conducted several alternative analyses. First, we excluded participants with a history of cancer at baseline. Second, to account for the possible influence of premortal disease or preclinical manifestations of glioma on baseline diet, we excluded the first 2 years of follow-up. Third, in place of the nutrient density method, we adjusted for energy intake using a standard multivariate model that included the daily consumption of the dietary intake of interest (not divided by 1,000 kcal), energy intake, and the other covariates.

Results

The mean age at baseline of cohort participants was 62.2 years. The cohort was well educated (38.6% college graduate/postgraduate) and predominantly non-Hispanic white (91.4%). During 3,908,867 person-years of follow-up (mean follow-up 7.2 years), 585 cases of glioma (419 among men and 166 among women) were identified. Age-adjusted, sex-specific incidence rates (U.S. 2000 standard population) for cancers of the brain and other nervous system in this cohort and the Surveillance, Epidemiology, and End Results registries (46) were similar (data not shown).

At baseline, high processed meat intake was associated with male sex (as indicated by the number of men versus women in each quintile of intake), lower level of education, lower intake of nitrate and fruit and vegetables, and higher red meat intake (Table 1). High fruit and vegetable intake was associated with female sex (as indicated by the number of women versus men in each quintile of intake), higher

level of education, lower intake of energy and processed and red meat, and higher intake of nitrite and nitrate.

In Table 2, we tested the hypotheses that processed and red meat intake increase glioma risk and that fruit and vegetable intake decreases glioma risk. We found no evidence for a positive association between intake of processed or red meat or of individual processed meat components (bacon, cold cuts, hot dogs, sausage; data not shown) and glioma risk. However, we observed fruit and vegetable intake to be positively associated with glioma risk [HR for quintile 5 (Q5) versus Q1, 1.42; 95% CI, 1.08-1.86, *P* for trend = 0.0081]. This association was driven more by whole fruit intake than by vegetable intake, with no contribution from fruit juices. Mutual adjustment of whole fruit intake and vegetable intake did not substantially change this finding (data not shown). The relationship between whole fruit intake and glioma risk varied significantly by sex (*P* for sex interaction = 0.025), with the association observed in men but not in women. We found no significant trends of glioma risk with respect to consumption of each of 13 botanical subgroups of fruit and vegetables (data not shown).

In Table 3, we tested the hypotheses that nitrite and nitrate intake increase glioma risk. We observed a borderline-significant trend of increasing glioma risk with increasing nitrite intake (Q5 versus Q1, 1.32; 95% CI, 1.01-1.71, *P* for trend = 0.089), which was driven by intake of nitrite from plant sources (Q5 versus Q1, 1.59; 95% CI, 1.20–2.10; *P*-trend = 0.028). HRs for intake of nitrite from plant sources were significantly elevated for Q2 to Q5, with no trend of increasing risk between Q2 to Q5. Of the top five foods that together contributed 42.7% of intake of nitrite from plant sources in this cohort (pasta, rice/grains, white breads/rolls, hot breakfast cereals, and apples), only intake of rice/grains exhibited a significant trend (tertile 3 versus tertile 1, 1.24; 95% CI, 1.01–1.52; *P* for trend = 0.042). The relationship between intake of nitrite from plant sources and glioma risk varied significantly by sex (*P* for sex interaction = 0.030), with the association observed in men but not in women (Table 3).

We did not observe a significant trend for glioma risk in relation to nitrate intake (Table 3). We observed no suggestion of a positive association between glioma risk and intake of nitrite or nitrate from animal sources (Table 3), or nitrite plus nitrate from processed meat (Table 3) or animal sources (data not shown).

Excluding the 13,069 cohort members who might have had nitrate exposure from drinking water above the maximum contaminant level (10 mg/L) did not meaningfully change the results in Table 3 (data not shown). Estimating intake of nitrite and nitrate from processed meat sources using the database based on measurements done on processed meats purchased in 2004 did not meaningfully change the results for intake of nitrite plus nitrate from processed meat sources (data not shown).

In Table 4, we tested the hypotheses that intake of the nitrosation inhibitors vitamin C and vitamin E decreases glioma risk. We observed no significant trends in glioma risk in relation to intake of vitamin C or E. Mutual adjustment for dietary and supplemental vitamin C intake or dietary and supplemental vitamin E intake did not meaningfully change the results (data not shown).

To test for possible mutual confounding between intake of fruit and vegetables and nitrite from plant sources, we created a final multivariate model in which we mutually adjusted for these intakes. Compared with the models that were not mutually adjusted, in this model, the association between intake of each of these items and glioma risk was attenuated (fruit and vegetable intake, Q5 versus Q1, 1.30; 95% CI, 0.95–1.76; *P* for trend = 0.071; intake of nitrite from plant sources, Q5 versus Q1, 1.39; 95% CI, 1.02–1.90; *P* for trend = 0.31).

The NOC hypothesis predicts that nitrosation inhibitor intake will modify the relationship between nitrite/nitrate intake and glioma risk such that persons with high intake of nitrite and/or nitrate in combination with low intake of nitrosation inhibitors would have synergistically higher risk than persons with low intake of nitrite and/or nitrate in combination with high intake of nitrosation inhibitors (12). However, we found no evidence for the predicted interactions of nitrite/nitrate intake with dietary vitamin C intake (Table 5) or with intake of vitamin C from supplemental sources, vitamin E from dietary or supplemental sources, or fruit and vegetables (data not shown). Although we observed a significant interaction between intake of both total nitrite and nitrite from plant sources and dietary vitamin E intake, the pattern of effect modification was inconsistent with that predicted by the NOC hypothesis (data not shown).

The NOC hypothesis also predicts that nitrosation promoters will modify the relationship between nitrite and nitrate intake and glioma risk such that persons with high intake of nitrite and/or nitrate in combination with high intake of red meat (nitrosation promoter) would have synergistically higher risk than persons with low intake of nitrite and/or nitrate in combination with low intake of nitrosation promoters. However, we found no evidence for the predicted interactions between nitrite/nitrate intake and red meat intake (data not shown). Although we observed a significant interaction between intake of total nitrite, total nitrate, and nitrite plus nitrate from animal sources and red meat intake, the pattern of effect modification was inconsistent with that predicted by the NOC hypothesis (data not shown).

In Table 6, we tested the hypothesis that a diet resulting in high exposure to NOCs during adolescence (ages 12–13 years) increases adult glioma risk. For intake of nitrite plus nitrate from processed meat at ages 12 to 13 years, the HR was significantly elevated for Q4 versus Q1, but not for Q5 versus Q1, with no evidence for a trend. Results were similar for processed meat intake at ages 12 to 13 years. Dietary vitamin C and red meat consumption at ages 12 to 13 years were unrelated to glioma risk. We observed no evidence for

Table 2. Multivariate HR and 95% CI according to quintile of meat or fruit and vegetable intake and glioma risk

Meat or fruit and vegetable intake	Quintile of intake					*P* for trend	*P* for sex interaction
	Q1	Q2	Q3	Q4	Q5		
Processed meat							
Median intake*	0.08	0.17	0.28	0.43	0.78		
No. of cases	99	133	125	106	122		
Multivariate HR†	1.00	1.26	1.14	0.94	1.05	0.44	0.24
95% CI	(Reference)	0.97–1.64	0.88–1.49	0.71–1.24	0.80–1.37		
Red meat							
Median intake*	0.31	0.66	0.97	1.33	1.94		
No. of cases	114	117	131	113	110		
Multivariate HR†	1.00	0.98	1.06	0.89	0.85	0.15	0.21
95% CI	(Reference)	0.76–1.27	0.82–1.37	0.68–1.16	0.65–1.11		
Fruit and vegetables							
Median intake‡	1.12	1.69	2.17	2.75	3.81		
No. of cases	98	108	132	122	125		
Multivariate HR†	1.00	1.09	1.36	1.30	1.42	0.0081	0.46
95% CI	(Reference)	0.83–1.44	1.05–1.77	0.99–1.71	1.08–1.86		
Fruit							
Median intake‡	0.30	0.67	1.01	1.44	2.26		
No. of cases	108	105	127	126	119		
Multivariate HR†	1.00	0.96	1.17	1.18	1.16	0.14	0.12
95% CI	(Reference)	0.73–1.26	0.90–1.52	0.91–1.53	0.89–1.52		
Whole fruit							
Median intake‡	0.14	0.36	0.60	0.91	1.52		
No. of cases	108	104	111	127	135		
Multivariate HR†	1.00	0.95	1.03	1.21	1.34	0.0037	0.025
95% CI	(Reference)	0.73–1.25	0.79–1.35	0.93–1.57	1.04–1.75		
Whole fruit (males)							
No. of cases	79	74	85	89	92		
Multivariate HR†	1.00	0.97	1.19	1.39	1.70	<0.0001	
95% CI	(Reference)	0.71–1.33	0.87–1.62	1.02–1.88	1.25–2.31		
Whole fruit (females)							
No. of cases	29	30	26	38	43		
Multivariate HR†	1.00	0.87	0.65	0.80	0.75	0.39	
95% CI	(Reference)	0.52–1.46	0.38–1.10	0.49–1.30	0.47–1.21		
Fruit juices							
Median intake‡	0.02	0.11	0.30	0.52	1.01		
No. of cases	118	107	124	125	111		
Multivariate HR†	1.00	0.90	1.03	1.02	0.94	0.90	0.98
95% CI	(Reference)	0.69–1.17	0.80–1.32	0.80–1.32	0.72–1.22		
Vegetables							
Median intake‡	0.55	0.82	1.06	1.34	1.92		
No. of cases	104	112	118	139	112		
Multivariate HR†	1.00	1.06	1.13	1.37	1.17	0.11	0.99
95% CI	(Reference)	0.81–1.39	0.87–1.48	1.06–1.77	0.89–1.53		

*MPED ounce equivalents/1,000 kcal/d.

†Adjusted for sex, age (continuous), race (non-Hispanic white, non-Hispanic black, other, and missing), energy intake (continuous), education (<high school, high school graduate, post–high school other than college, some college, college graduate, postgraduate, and missing), height (eight prespecified categories and missing), and history of cancer at baseline (yes, no, and missing).

‡MPED cup equivalents/1,000 kcal/d.

Table 3. Multivariate HR and 95% CI according to quintile of nitrite and nitrate intake and glioma risk

Nitrite or nitrate intake	Quintile of intake					*P* for trend	*P* for sex interaction
	Q1	Q2	Q3	Q4	Q5		
Nitrite							
Median intake*	0.45	0.57	0.65	0.74	0.90		
No. of cases	101	129	106	118	131		
Multivariate HR†	1.00	1.25	1.03	1.16	1.32	0.089	0.32
95% CI	(Reference)	0.96–1.63	0.79–1.36	0.89–1.52	1.01–1.71		
Plant sources							
Median intake*	0.25	0.34	0.42	0.51	0.68		
No. of cases	87	142	117	112	127		
Multivariate HR†	1.00	1.62	1.36	1.35	1.59	0.028	0.030
95% CI	(Reference)	1.24–2.12	1.03–1.80	1.01–1.79	1.20–2.10		
Plant sources (males)							
No. of cases	59	113	84	77	86		
Multivariate HR†	1.00	2.02	1.61	1.63	2.04	0.0026	
95% CI	(Reference)	1.47–2.77	1.15–2.25	1.16–2.30	1.46–2.87		
Plant sources (females)							
No. of cases	28	29	33	35	41		
Multivariate HR†	1.00	0.84	0.84	0.79	0.84	0.57	
95% CI	(Reference)	0.50–1.41	0.51–1.40	0.48–1.30	0.51–1.36		
Animal sources							
Median intake*	0.10	0.15	0.20	0.25	0.36		
No. of cases	123	112	119	107	124		
Multivariate HR†	1.00	0.87	0.91	0.80	0.90	0.45	0.11
95% CI	(Reference)	0.68–1.13	0.71–1.17	0.62–1.04	0.70–1.16		
Nitrate							
Median intake*	19.35	29.92	40.95	57.40	94.85		
No. of cases	98	114	135	126	112		
Multivariate HR†	1.00	1.16	1.41	1.37	1.28	0.14	0.99
95% CI	(Reference)	0.89–1.52	1.09–1.84	1.05–1.79	0.97–1.70		
Plant sources							
Median intake*	16.56	27.03	38.01	54.49	92.06		
No. of cases	101	109	136	125	114		
Multivariate HR†	1.00	1.08	1.38	1.31	1.26	0.12	0.98
95% CI	(Reference)	0.82–1.41	1.06–1.79	1.01–1.71	0.96–1.67		
Animal sources							
Median intake*	1.51	2.17	2.69	3.28	4.34		
No. of cases	119	125	121	105	115		
Multivariate HR†	1.00	1.02	0.99	0.88	1.03	0.86	0.32
95% CI	(Reference)	0.80–1.31	0.77–1.28	0.68–1.15	0.79–1.33		
Nitrite plus nitrate							
Processed meat sources							
Median intake*	0.11	0.29	0.49	0.77	1.43		
No. of cases	100	121	135	109	120		
Multivariate HR†	1.00	1.15	1.24	0.97	1.04	0.56	0.79
95% CI	(Reference)	0.88–1.50	0.95–1.61	0.74–1.28	0.79–1.36		

*mg/1,000 kcal/d.

†Adjusted for sex, age (continuous), race (non-Hispanic white, non-Hispanic black, other, and missing), energy intake (continuous), education (<high school, high school graduate, post–high school other than college, some college, college graduate, postgraduate, and missing), height (eight prespecified categories and missing), and history of cancer at baseline (yes, no, and missing).

Table 4. Multivariate HR and 95% CI according to category of vitamin C and vitamin E intake and glioma risk

Vitamin intake	Category of intake					*P* for trend	*P* for sex interaction
Vitamin C, dietary	Q1	Q2	Q3	Q4	Q5		
Median intake*	35	59	80	107	160		
No. of cases	98	113	143	116	115		
Multivariate HR†	1.00	1.15	1.47	1.22	1.26	0.19	0.89
95% CI	(Reference)	0.87–1.50	1.14–1.91	0.93–1.61	0.96–1.66		
Vitamin C, supplemental‡	0	>0–99	100–499	500–999	≥1,000		
Median intake‡	0	60	203	560	1,060		
No. of cases	189	104	106	105	81		
Multivariate HR†	1.00	0.93	1.40	1.34	1.09	0.19	0.15
95% CI	(Reference)	0.73–1.19	1.10–1.78	1.06–1.70	0.84–1.41		
Vitamin E, dietary	Q1	Q2	Q3	Q4	Q5		
Median intake§	6.2	7.6	8.6	9.8	12.1		
No. of cases	108	109	122	127	119		
Multivariate HR†	1.00	1.01	1.15	1.23	1.17	0.12	0.042
95% CI	(Reference)	0.77–1.31	0.89–1.49	0.95–1.59	0.90–1.53		
Vitamin E, dietary (males)							
No. of cases	84	89	86	95	65		
Multivariate HR†	1.00	1.13	1.17	1.41	1.04	0.50	
95% CI	(Reference)	0.84–1.52	0.87–1.58	1.05–1.89	0.75–1.44		
Vitamin E, dietary (females)							
No. of cases	24	20	36	32	54		
Multivariate HR†	1.00	0.66	1.04	0.83	1.28	0.072	
95% CI	(Reference)	0.36–1.19	0.62–1.74	0.49–1.40	0.79–2.07		
Vitamin E, supplemental‖	0	>0–99	100–399	400–799	≥800		
Median intake‖	0	30	221	430	830		
No. of cases	195	169	57	133	31		
Multivariate HR†	1.00	1.09	1.05	1.27	1.02	0.27	0.42
95% CI	(Reference)	0.89–1.34	0.78–1.41	1.02–1.58	0.70–1.49		

*mg/1,000 kcal/d.

†Adjusted for sex, age (continuous), race (non-Hispanic white, non-Hispanic black, other, and missing), energy intake (continuous), education (<high school, high school graduate, post–high school other than college, some college, college graduate, postgraduate, and missing), height (eight prespecified categories and missing), and history of cancer at baseline (yes, no, and missing).

‡mg/d.

§IU/1,000 kcal/d.

‖IU/d.

interaction between intake of nitrite plus nitrate from processed meat at ages 12 to 13 years and intake of dietary vitamin C (Table 6) or red meat (data not shown) at ages 12 to 13 years.

Finally, we repeated all analyses presented in Tables 2 to 6 in three different ways: we excluded 50,778 participants with a history of cancer at baseline; we excluded the first 2 years of follow up; and in place of the nutrient density method, we adjusted for energy intake by including it in the model without normalizing dietary intake according to energy intake. Results of these analyses did not meaningfully differ from the results of our main analyses, with one exception: When adjusting for energy intake without normalizing dietary intake according to energy intake, we observed a significant trend of increasing risk with increasing processed meat intake at ages 12 to 13 years.

Discussion

This is only the second large prospective cohort study to perform a thorough, multifaceted examination of the

Table 5. Multivariate HR and 95% CI according to low/high joint intake of nitrite or nitrate and vitamin C and glioma risk

Joint intake Nitrite and/or nitrate/vitamin C	Low/high	Low/low	High/high	High/low	*P* for joint interaction
Nitrite, total, median intake*	0.55	0.55	0.77	0.77	
Dietary vitamin C, median intake*	116	53	116	53	
No. of cases	133	155	175	122	
Multivariate HR†	1.00	0.85	1.01	0.88	0.88
95% CI	(Reference)	0.67–1.08	0.81–1.27	0.69–1.13	
Nitrite, plant sources, median intake*	0.32	0.32	0.54	0.54	
Dietary vitamin C, median intake*	116	53	116	53	
No. of cases	125	164	183	113	
Multivariate HR†	1.00	0.77	0.93	0.91	0.16
95% CI	(Reference)	0.61–0.98	0.74–1.18	0.71–1.18	
Males					
No. of cases	87	129	118	85	
Multivariate HR†	1.00	0.78	1.00	0.97	0.29
95% CI	(Reference)	0.59–1.03	0.76–1.32	0.72–1.31	
Nitrate, total, median intake*	27.4	27.4	63.5	63.5	
Dietary vitamin C, median intake*	116	53	116	53	
No. of cases	100	174	208	103	
Multivariate HR†	1.00	0.89	1.17	1.07	0.87
95% CI	(Reference)	0.69–1.14	0.92–1.49	0.81–1.41	
Nitrite plus nitrate, animal sources, median intake*	2.2	2.2	3.7	3.7	
Dietary vitamin C, median intake*	116	53	116	53	
No. of cases	173	132	135	145	
Multivariate HR†	1.00	0.82	0.90	0.83	0.50
95% CI	(Reference)	0.65–1.03	0.72–1.13	0.66–1.03	
Nitrite plus nitrate, processed meat sources, median intake*	0.25	0.25	0.87	0.87	
Dietary vitamin C, median intake*	116	53	116	53	
No. of cases	182	114	126	163	
Multivariate HR†	1.00	0.89	0.93	0.79	0.80
95% CI	(Reference)	0.70–1.13	0.74–1.17	0.64–0.99	

NOTE: Low/high distinctions were based on median intake values.

*mg/1,000 kcal/d.

†Adjusted for sex, age (continuous), race (non-Hispanic white, non-Hispanic black, other, and missing), energy intake (continuous), education (<high school, high school graduate, post–high school other than college, some college, college graduate, postgraduate, and missing), height (eight prespecified categories and missing), and history of cancer at baseline (yes, no, and missing).

NOC hypothesis in relation to dietary factors and adult glioma risk. Consistent with the combined results of the Health Professionals Follow-up Study and Nurses' Health Studies (20, 22), we did not observe significant trends of increasing glioma risk with increasing intake of processed or red meat, nitrite, or nitrate, and we found no evidence that intake of fruit and vegetables, fruit and vegetable subgroups, vitamin C, or vitamin E decreases glioma risk. Furthermore, examination of interactions between dietary intakes provided no support for our hypotheses. Similarly, in the Health Professionals Follow-up/Nurses' Health Studies, no interactions were observed between intake of processed meat and vitamins C or E or an estimate of the ferric-reducing ability of plasma (using dietary intake to represent the total antioxidant capacity of foods) (22). Furthermore, in the Health Professionals Follow-up/Nurses' Health Studies, glioma risk was unrelated to dietary intake of two nitrosamines (nitrosodimethylamine and nitrosopyrolidine), estimated by linking FFQ data with a database of values for these compounds derived from the literature (22).

Thus, the weight of the evidence from our study and the Health Professionals Follow-up/Nurses' Health Studies calls into question the NOC hypothesis, at least at the dietary intake levels of these populations. Research suggesting that both exposure to cigarette smoke (which contains NOCs, although nitrosamines, not nitrosamides) (44, 45) and ingestion of nitrate from drinking water (47, 48) are unrelated to adult glioma risk calls this hypothesis into question as well.

Although we observed a significant positive association between adult intake of nitrite from plant sources and glioma risk, this association was attenuated by

Table 6. Multivariate HR and 95% CI according to dietary intakes at ages 12 to 13 years and glioma risk

Intake	Quintile of intake					*P* for trend	*P* for sex interaction
	Q1	Q2	Q3	Q4	Q5		
Processed meat							
Median intake*	5.4	13.5	21.1	30.2	45.5		
No. of cases	59	55	49	91	64		
Multivariate HR†	1.00	0.91	0.80	1.41	0.97	0.45	0.54
95% CI	(Reference)	0.63–1.32	0.54–1.17	1.00–1.99	0.66–1.40		
Nitrite plus nitrate, processed meat sources							
Median intake‡	0.37	0.99	1.70	2.51	3.94		
No. of cases	55	59	49	86	69		
Multivariate HR†	1.00	1.05	0.86	1.47	1.16	0.16	0.44
95% CI	(Reference)	0.72–1.52	0.58–1.28	1.03–2.08	0.80–1.67		
Red meat							
Median intake*	22.1	39.0	51.5	64.7	85.7		
No. of cases	61	54	62	72	69		
Multivariate HR†	1.00	0.86	0.98	1.13	1.08	0.33	0.55
95% CI	(Reference)	0.60–1.25	0.68–1.40	0.79–1.60	0.76–1.54		
Dietary vitamin C							
Median intake‡	17	25	36	54	84		
No. of cases	63	66	68	58	63		
Multivariate HR†	1.00	1.04	1.07	0.93	1.03	0.93	0.63
95% CI	(Reference)	0.73–1.47	0.76–1.51	0.65–1.33	0.72–1.47		

Joint intake§

Nitrite plus nitrate/dietary vitamin C	Low/high	Low/low	High/high	High/low	*P* for joint interaction
Nitrite plus nitrate, processed meat sources, median intake‡	0.84	0.84	2.77	2.77	
Dietary vitamin C, median intake‡	59	23	59	23	
No. of cases	72	67	77	102	
Multivariate HR†	1.00	1.01	1.12	1.32	0.50
95% CI	(Reference)	0.73–1.42	0.81–1.56	0.97–1.81	

*g/1,000 kcal/d (where kcal is based on energy intake at ages 12–13 years).

†Adjusted for sex, age (continuous), race (non-Hispanic white, non-Hispanic black, other, and missing), energy intake at baseline (continuous), education (<high school, high school graduate, post–high school other than college, some college, college graduate, postgraduate, and missing), height (eight prespecified categories and missing), history of cancer at baseline (yes, no, and missing), energy intake at ages 12 to 13 years (continuous), BMI at age 18 years (five prespecified categories and missing), and physical activity at ages 15 to 18 years (quintiles of metabolic equivalent hours per week and missing).

‡mg/1,000 kcal/d (where kcal is based on energy intake at ages 12–13 years).

§Low/high distinctions were based on median intake values.

inclusion of fruit and vegetable intake in the multivariate model. Furthermore, the association was only observed in males, and no trend of increasing risk was observed between Q2 and Q5. Finally, there is no reason to expect plant sources to preferentially result in increased endogenous NOC formation compared with animal sources (47). In fact, it has been proposed that intake of nitrite (and nitrate) from fruit and vegetable sources confers little or no glioma risk due to the presence of nitrosation inhibitors in these foods, resulting in little endogenous NOC formation (12). Nevertheless, this result should not be totally dismissed. Grain products are a major contributor to nitrite from plant sources; unlike fruit and vegetables, grain products do not contain large amounts of nitrosation inhibitors, allowing for the possibility of endogenous NOC formation resulting from consumption of nitrite from grain sources. In addition, the current result is consistent with a case-control study that also found a positive association between intake of nitrite from plant sources, but not from animal sources, and glioma risk (47). Finally, because we did not adjust significance levels for multiple comparisons, we cannot rule out that our finding that the association was restricted to males (P for sex interaction = 0.030) was due to chance. Given these considerations, and because nitrite and nitrate intakes by source were not examined in the Health Professionals Follow-up/Nurses' Health Studies, these relationships should be investigated in future prospective studies.

We observed an unexpected finding of increasing glioma risk with increasing intake of fruit and vegetables. This association was driven more by whole fruit consumption than by vegetable consumption; the association between whole fruit intake and glioma risk was only observed in males. Interestingly, for fruit intake, a HR of 1.41 (95% CI, 0.95–2.10) for Q5 versus Q1, with a P value for trend of 0.12, was observed in the Health Professionals Follow-up/Nurses' Health Studies (20). Because increased brain cancer risk has been observed in farmers (49), who are exposed to pesticides; in pesticide applicators exposed to chlorpyrifos, a widely used organophosphate agricultural insecticide (50); and in farmers with poor pesticide-related work practices (51), one can speculate that the association we observed between fruit and vegetable intake and glioma risk may be due to pesticide residues consumed with fruit and vegetables. Thus, it might be informative to pursue this finding in future prospective studies.

It has been proposed that intake of vitamins C and E might protect against brain cancer risk due to their potency as antioxidants, independent of their antinitrosation properties (3, 7). Similarly, consumption of fruit and vegetables, which are rich sources of antioxidants, polyphenols, and other phytochemicals that may act synergistically as anticarcinogens through a variety of mechanisms other than nitrosation inhibition (52), has been postulated to reduce brain cancer risk (3, 4, 7). Our results provide no support for these hypotheses.

We hypothesized that a diet resulting in high exposure to NOCs during adolescence may increase adult glioma risk. In animals, NOCs exert their most potent neurocarcinogenic effect early in life (1). In addition, high BMI during adolescence and physical inactivity during adolescence were previously found to be associated with increased glioma risk in the NIH-AARP Diet and Health Study cohort, supporting a role for early life events in glioma carcinogenesis (23). Although we found little support for our hypothesis, our analysis was limited by the brevity of the FFQ used to assess diet at ages 12 to 13 years, by the smaller sample size for this analysis (only about 60% of participants returned this questionnaire), and by uncertainty about the validity of measurement of dietary intake many years in the past (53). Thus, further work may be warranted.

Nevertheless, our results, together with those of the Health Professionals Follow-up/Nurses' Health Studies, suggest that dietary factors may have little influence on adult glioma risk. International variation in malignant brain tumor incidence has been found to be substantially less than that observed for many other types of cancer (3, 7, 54), suggesting that glioma risk may be driven more by genetic than by environmental factors such as diet.

This study had several limitations. Food and nutrient intake was measured via a FFQ, which is subject to measurement error (55). In addition, we did not attempt to directly estimate dietary intake of individual NOCs, as was done by the Health Professionals Follow-up/Nurses' Health Studies investigators (22). Furthermore, because the baseline FFQ queried about usual intake in the past year among persons ages 50 to 71 years at baseline and was administered only once, at baseline, with no repeated measures, our main dietary assessment may not have measured diet during the etiologically relevant exposure period. Finally, in this study, we performed multiple comparisons of dietary intakes, increasing the likelihood of type I errors.

This study also had strengths. It was the largest and only the second prospective cohort study to test the hypothesis that a diet resulting in higher exposure to NOCs increases adult glioma risk. The prospective design overcame many of the limitations of case-control studies mentioned previously. In addition, there was a wide range of intake of the foods and micronutrients of interest and we were able to control for potential confounders. Finally, the consistency of alternative analyses showed our results to be robust.

In summary, our results, in concert with the results from the Health Professionals Follow-up/Nurses' Health Studies (20, 22), suggest that consumption of processed or red meat, nitrite, or nitrate does not meaningfully increase adult glioma risk, and that consumption of fruit and vegetables, fruit and vegetable subgroups, vitamin C, or vitamin E does not meaningfully protect against adult glioma risk. These results cast doubt on the NOC hypothesis in relation to dietary intake and adult glioma. However, further work is needed to enhance estimation of dietary

intake of individual and total NOCs through improved FFQs (37) or the use of biomarkers, to take genetic susceptibility into account, and to determine whether early life diet, adult intake of nitrite from plant sources, or adult intake of fruit and vegetables influences adult glioma risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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