# Prospective study of meat intake and dietary nitrates, nitrites, and nitrosamines and risk of adult glioma[1–3]

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**ABSTRACT**

**Background:** The hypothesis that nitrosamine exposure may increase the risk of glioma has been circulating for several decades, but testing it has been difficult because of the ubiquitous nature of nitrosamine exposure. Diet has been the focus of many studies because it can substantially influence nitrosamine exposure, mostly from the endogenous formation of nitrosamines based on intake of nitrite and nitrate.

**Objective:** The objective was to examine the relation between intakes of meats, nitrate, nitrite, and 2 nitrosamines [nitrosodimethylamine (NDMA) and nitrosopyrolidine (NPYR)] and glioma risk in a prospective analysis.

**Methods:** Data from 3 US prospective cohort studies were combined for this analysis; 335 glioma cases were diagnosed during $\leq$24 y of follow-up. Dietary intake was assessed with food-frequency questionnaires. Nitrate, nitrite, and nitrosamine values were calculated based on published values of these nutrients in various foods over different periods in time. Cox proportional hazards models were used to estimate incidence rate ratios (RRs) and 95% CIs. Estimates from each cohort were pooled by using a random-effects model.

**Results:** Risk of glioma was not elevated among individuals in the highest intake category of total processed meats (RR: 0.92; 95% CI: 0.48, 1.77), nitrate (RR: 1.02; 95% CI: 0.66, 1.58), nitrites (RR: 1.26; 95% CI: 0.89, 1.79), or NDMA (RR: 0.88; 95% CI: 0.57, 1.36) compared with the lowest category. No effect modification was observed by intake of vitamins C or E or other antioxidant measures.

**Conclusion:** We found no suggestion that intake of meat, nitrate, nitrite, or nitrosamines is related to the risk of glioma. *Am J Clin Nutr* 2009;90:570–7.

## INTRODUCTION

*N*-Nitroso compounds (NOC) are broadly acting and potent carcinogens in animal models (1, 2). Furthermore, transplacental exposure to ethylnitrosourea (ENU)—a nitrosamide—results in the formation of brain tumors, including gliomas, in rodents (3). NOC can be present in food treated with sodium nitrite or can form endogenously if the nitrites react with secondary amines or amides (1). The endogenous formation of NOCs in the stomach is complex because it is influenced by various physiologic parameters, including gastric pH, the presence of bacteria, and antioxidants (4). NOCs have been detected in brain tissue and can cross the blood-brain barrier (5). Processed and cured meat intakes have been used as markers of NOC exposure. Because they contain high concentrations of nitrites and are often eaten on a daily basis, their total contribution to the overall level of NOCs can be substantial.

Many positive findings from studies examining the association between maternal intake of cured meats during pregnancy and the subsequent risk of childhood cancer (6) have provided incentive to examine these dietary exposures in relation to adult brain tumors. To date, findings from studies on dietary intake of meats, particularly processed meats, and the risk of adult gliomas have been inconsistent. However, a meta-analysis of 9 observational studies, mostly case-control studies, suggested that a positive association may exist [relative risk (RR): 1.48; 95% CI: 1.20, 1.83] for adult glioma among individuals with a high cured meat intake of all types, although total energy was not adjusted for in most studies (7). To our knowledge, only one prospective study has addressed this hypothesis to date, and only 21 glioma cases were included in that analysis (8).

This study was undertaken to examine the association between intake of total meat, processed meats, nitrosamine precursors (ie, nitrate, nitrite), and 2 nitrosamines [nitrosodimethylamine (NDMA) and nitrosopyrolidine (NPYR)] and the risk of glioma in 3 US prospective cohort studies.

## SUBJECTS AND METHODS

### Study populations

The Nurses' Health Study I (NHS I) was initiated in 1976, when 121,700 registered US female nurses aged 30–55 y returned a mailed questionnaire that assessed information on lifestyle

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[2] Supported by grant CA110948 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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Received November 5, 2008. Accepted for publication June 8, 2009.

First published online July 8, 2009; doi: 10.3945/ajcn.2008.27199.

 

factors, medical histories, and smoking histories (9). Similarly, the Health Professionals Follow-Up Study (HPFS) is a cohort of 51,529 US male physicians, dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians who were 40–75 y of age at enrollment in 1986 (10). The study design and methods of dietary assessment and follow-up for the Nurses' Health Study II (NHS II) are very similar to those of NHS I. In 1989, 116,686 women aged 25–42 y and living in 14 US states were enrolled in NHS II (11). Follow-up questionnaires are mailed biennially to all cohort members to update information on lifestyle factors, diet, and newly diagnosed medical conditions. The questionnaire response rate over the period of follow-up was 94% among women in the NHS I diet cohort (1980–2002) and was 92% among men in the HPFS (1986–2002). The follow-up rate for the cohorts for incidence of cancer was >95% of the total possible person-years.

Deaths of cohort members are frequently reported by family members or by the postal service in response to questionnaire mailings. In addition, the National Death Index is searched biennially for nonrespondents; this method has been shown to have a sensitivity of 98% (12). This study was approved by the Human Research Committee of the Brigham and Women's Hospital.

### Dietary assessment

To assess dietary intake, food-frequency questionnaires (FFQs) were initially collected in 1986 for 49,935 men (HPFS), in 1980 for 92,468 women (NHS I), and in 1991 for 95,391 women (NHS II), and diet was generally updated every 4 y. For the NHS I, we used a 61-item semiquantitative FFQ (including dietary items and vitamin use) at baseline in 1980, which was expanded to ≈130 items (including food, beverages, and vitamin use) in 1984, 1986, and every 4 y thereafter. For the HPFS and NHS II cohorts, baseline dietary intake was assessed by using a 131-item FFQ. The questions on meat intake (other than fish) were very similar on the 61-item FFQs and the 131-item FFQs; both had the same number of questions with similar meat items included in each.

For each item, participants were asked to report their average use over the preceding year for a specified serving size of each food and beverage. Nine prespecified frequency responses were possible, ranging from never or almost never to ≥6 times/d. Individual nutrient intakes were calculated by multiplying the frequency of each food or beverage consumed by the nutrient content of the specified portion size and then by summing the contributions from all foods and beverages. Food composition data were primarily based on values obtained from the US Department of Agriculture supplemented with our own data. For vitamins C and E, calculations were based on dietary intake and vitamin supplement use (current use and dose of vitamin supplements and the brand and type of multivitamins). We also estimated the ferric-reducing ability of plasma (FRAP) using dietary intake to represent the total antioxidant capacity of foods. The FRAP assay measures the reduction of $Fe^{3+}$ (ferric ion) to $Fe^{2+}$ (ferrous ion) in the presence of antioxidants and expresses the corresponding concentration of hydrogen- or electron-donating antioxidants (13, 14). Data on FRAP from plant foods were gathered from published databases.

In addition, we searched the literature for publications with food values for nitrate, nitrite, NDMA, and NPYR and derived a database with values for these compounds for each of the cohort baseline FFQs, accounting for changes in values over time due to changes in processing practices to lower nitrosamine concentrations (15–39). To calculate these compounds, we first considered publications in which measurements in foods were made closest in time to the questionnaire year and preferably in the United States. If food values were not available from that time period or from the United States, we used measurements made in foods at different times or from Europe. For foods with more than one available measurement (from one or more publications), we estimated the weighted average value of the compounds (based on number of food samples tested) and used those values for our calculations.

Intakes of meat were calculated by multiplying the frequency of intake for individual items by their weights, which were estimated from the specified portion size (and by using additional data from the validation studies to determine mean values for portion size to verify that the specified sizes were accurate). Total meat consisted of the following food items: processed meats (eg, sausage, salami, and bologna); bacon; hot dogs; hamburger; beef, pork, or lamb in a sandwich or mixed dish; beef, pork, or lamb as a main dish; chicken or turkey with skin; and chicken or turkey without skin. Red meat consisted of total meat minus chicken or turkey. Total processed meats consisted of the processed meat item (eg, sausage, salami, and bologna) plus bacon and hot dogs.

The reproducibility and validity of food and beverage intake were described previously for the HPFS (40, 41) and NHS I (42). In the HPFS, Pearson correlations between the average intake assessed by two 1-wk diet records completed 6 mo apart, and the FFQ ranged from 0.56 for chicken or turkey without skin to 0.83 for processed meat (40). In NHS I, the correlations between the diet records (corrected for within-person variation) and FFQ were 0.70 for bacon, 0.56 for hot dogs, 0.55 for processed meats, 0.46 for meat (from a main dish or mixed dish), and 0.38 for hamburgers (42). Vitamin E intake was positively correlated with its plasma concentrations in women ($r$ = 0.41) (43). Correlation coefficients between intakes from the FFQs and the average of two to four 1-wk diet records for vitamin C was 0.75 in women (44) and 0.92 for both total vitamins C and E in men (41).

### Case ascertainment

On each biennial questionnaire, the participants were asked whether they had received a diagnosis of cancer, heart disease, or other medical conditions during the previous 2 y. When permission was received from the cases (or next of kin for decedents), medical records and pathology reports were obtained from hospitals and reviewed by study investigators, who were blinded to the questionnaire data. Nonrespondents were telephoned in an attempt to confirm the initial cancer report and date of diagnosis. Medical records and pathology reports were requested for reported and deceased glioma cases; ≈88% of potential cases (ie, self-reported or deceased cases with glioma) were subsequently confirmed with medical, pathology, or cancer registry data. When we were unable to obtain records, we attempted to corroborate diagnoses of glioma with additional information from the participant or next of kin. We only included glioma cases for which a medical, pathology, or death record or other confirmation of the cancer was obtained. We included all glioma brain tumors; these included astrocytoma [International

Classification of Diseases for Oncology (ICD-O) codes 9400, 9401, and 9411 (45)], glioblastoma (9440, 9441, and 9442/3), oligodendroglioma (9450, 9451, and 9460), ependymoma (9391, 9392, 9393, and 9394), mixed glioma subtypes (9382), and glioma, NOS (9380).

We identified 133 newly diagnosed gliomas between 1986 and 2004 among men, 182 gliomas among women in the NHS I between 1980 and 2004, and 20 gliomas among women in the NHS II between 1991 and 2005.

### Statistical analysis

Person-time of follow-up was calculated from the date for return of the baseline FFQ (1980 for NHS I, 1986 for HPFS, and 1991 for NHS II) until the date of glioma diagnosis, date of death from any cause, or the end of follow-up (31 December 2004 for HPFS, 31 May 2004 for NHS I, and 31 May 2005 for NHS II), whichever came first. We excluded participants who reported a history of cancer other than nonmelanoma skin cancer at baseline or those with implausibly high or low daily caloric intakes ($<$800 or $>$4200 kcal/d for men; $<$500 or $>$3500 kcal/d for women). After these exclusions (which takes care of poor responders), any individual dietary questionnaire item that was missing an entry was coded as not being consumed by participant (because our validation studies have confirmed that most foods with missing responses on the FFQ are not consumed by the participants). Consequently there were no missing values for the estimated nutrients and vitamins. Missing values for the individual meat items ranged between 0.70% and 2.9% in the HPFS and between 0.3% and 1.0% in the NHS. The cohorts for analyses included 47,897 (96%) men in the HPFS followed for up to 18 y, 88,795 (96%) women in the NHS I who were followed for up to 24 y, and 93,963 (99%) women in the NHS II who were followed for up to 14 y.

Cox proportional hazards models for failure-time data were used to estimate the incidence rate ratio (RR) and 95% CI for glioma risk and to adjust for potential confounders. All models were stratified by age (continuous in months) and calendar year. In addition, we included total caloric intake in all models because it minimizes extraneous variation introduced by underreporting or overreporting in the FFQ (46). Additional analyses were conducted to check for potential confounding by total (dietary and supplement) vitamins C or E intakes (quintiles) and combined coffee and tea intake (categories: $<$2, 2, 3, 4, and $>$4 cups/d, given an association for this variable in these cohorts; 1 cup = 237 mL). Other factors typically considered as potential confounders in cancer analyses (eg, smoking, BMI, and fruit and vegetables) were not included in the models because they are not risk factors for glioma in these cohorts (47, 48). Furthermore, social class and education are fairly homogeneous in these cohorts because they are all health professionals.

For the meat analyses, we conducted baseline analyses (based on baseline FFQs) and updated dietary intakes with diet from subsequent questionnaires (in 1984, 1986, 1990, 1994, 1998, and 2002 in NHS I; in 1990, 1994, 1998, and 2002 in HPFS; and in 1995, 1999, and 2003 in NHS II). In these analyses, we assessed glioma risk in relation to the cumulative average of diet calculated from all of the preceding dietary questionnaires. The use of cumulative averages may reduce within-person subject variation and better represent long-term average intake (49). For example in the HPFS, dietary data from the 1986 FFQ was used for follow-up from 1986 to 1990, the average dietary intake from the 1986 and 1990 FFQs was used for follow-up from 1990 to 1994, and so forth. Because nitrite and nitrosamine databases were only created for the baseline questionnaires, we did not conduct updated analyses for the nutrients.

Tests of linear trend were conducted by assigning the median values for each and treating those as a single continuous variable with Cox proportional hazards regression. Because of the small number of glioma cases observed in the NHS II, the NHS I and NHS II cohorts were combined; the results in the women reflect the pooled estimates of the 2 cohorts. Quintiles for groups of foods or nutrients were created based on their distribution in each cohort study before the results were pooled; therefore, cutoffs vary by cohort. For bacon and hot dogs, the categories were based on the intake categories provided on the FFQs. Before pooling with the use of meta-analysis, tests of heterogeneity of the main exposures by cohort were performed by using the $Q$ statistic, and data were pooled by using a random-effects model for the log of the RR (50); no statistically significant heterogeneity was observed unless noted otherwise. All reported $P$ values are 2-tailed. All of the statistical procedures were performed by using SAS version 8 (SAS Institute Inc, Cary, NC).

## RESULTS

In all 3 cohorts, individuals with the highest intake of processed meat had elevated intakes of nitrite and nitrosamines and lower intakes of vitamin C, vitamin E, and folate compared with those in the lowest category of processed meat intake (**Table 1**). Men and women who had higher intakes of processed meats were more likely to be current smokers than were those who had lower intakes. Coffee and alcohol intakes were positively associated with processed meat intake in the HPFS and NHS I cohorts, but not in the NHS II cohort. Age, height, and BMI did not vary appreciably across categories of processed meat consumption in all 3 cohorts, although there were small differences that were statistically significant.

We examined total meat intake and different processed meats in relation to glioma risk in each cohort separately but present only pooled results because there was no heterogeneity across the cohorts (**Table 2** and **Table 3**). No associations were observed for total meat, red meat, processed meat, bacon, or hot dogs and risk of glioma in these cohorts. The analyses were similar when using baseline diet (data not shown) and when modeling the cumulative average for meat intake over the follow-up years in each cohort (Tables 2 and 3). All models included age and calories; other covariates, including intakes of vitamins C and E and coffee/tea did not modify the associations ($<$10% change in RR).

To explore the possibility that dietary nitrosamines (preformed) and nitrosamine precursors (ie, nitrates and nitrites) might be related to risk of glioma, we examined associations with nitrate, nitrites, and 2 common dietary nitrosamines (NDMA and NPYR). The estimated NDMA concentrations were higher in the NHS I cohort because beer still contained NDMA in 1980 (baseline diet); NDMA concentrations in beer were lower in the early 1980s as a result of changes in beer processing. Main dietary contributors to nitrate intake were green-leafy vegetables; for nitrites, skim milk, orange juice, processed meats, and hot

**TABLE 1**
Baseline characteristics by processed meat intake among men in the Health Professionals Follow-Up Study (HPFS; 1986) and women in the Nurses' Health Study I (NHS I; 1980) and NHS II (1991)[1]

| | Processed meats (quintile)[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Men, HPFS | | | Women, NHS I | | | Women, NHS II | | |
| Characteristic | 1 | 3 | 5 | 1 | 3 | 5 | 1 | 3 | 5 |
| No. of individuals | 8641 | 10,880 | 8889 | 8989 | 21,757 | 22,385 | 17,961 | 20,502 | 18,556 |
| Processed meats (g/d) | 0.14 ± 0.3[3] | 5.9 ± 1.0 | 27 ± 13.6 | 0 ± 0 | 5.2 ± 1.0 | 23 ± 12 | 0 ± 0 | 4.7 ± 0.7 | 18 ± 9.2 |
| Age (y) | 56 ± 9.9 | 54 ± 9.8 | 54 ± 9.5 | 49 ± 7.0 | 47 ± 7.2 | 46 ± 7.1 | 37 ± 4.6 | 37 ± 4.7 | 36 ± 4.6 |
| Height (in)[4] | 70 ± 2.7 | 70 ± 2.7 | 70 ± 2.7 | 64 ± 3.2 | 64 ± 3.4 | 64 ± 3.2 | 65 ± 2.6 | 65 ± 2.6 | 65 ± 2.6 |
| BMI (kg/m$^2$) | 25 ± 2.9 | 26 ± 3.1 | 26 ± 3.4 | 24 ± 4.1 | 24 ± 4.2 | 25 ± 4.7 | 24 ± 4.6 | 25 ± 5.3 | 26 ± 6.0 |
| Past smoker (%) | 42 | 45 | 44 | 33 | 28 | 25 | 25 | 21 | 20 |
| Current smoker (%) | 5 | 9 | 15 | 22 | 29 | 32 | 9 | 12 | 15 |
| Pack-years of cigarettes[5] | 23 | 25 | 28 | 45 | 41 | 41 | 11 | 12 | 13 |
| Daily dietary intake | | | | | | | | | |
| NDMA ($\mu$g) | 0.06 ± 0.04 | 0.07 ± 0.04 | 0.09 ± 0.05 | 0.09 ± 0.22 | 0.11 ± 0.26 | 0.11 ± 0.24 | 0.06 ± 0.03 | 0.06 ± 0.02 | 0.07 ± 0.02 |
| NPYR ($\mu$g) | 0.01 ± 0.007 | 0.03 ± 0.03 | 0.07 ± 0.09 | 0.01 ± 0.002 | 0.02 ± 0.02 | 0.05 ± 0.06 | 0.01 ± 0.002 | 0.02 ± 0.01 | 0.04 ± 0.05 |
| Nitrite (mg) | 1.6 ± 0.4 | 1.6 ± 0.3 | 2.1 ± 0.6 | 1.4 ± 0.4 | 1.3 ± 0.4 | 1.6 ± 0.4 | 1.9 ± 0.5 | 2.0 ± 0.4 | 2.4 ± 0.5 |
| Nitrate (mg) | 183 ± 122 | 150 ± 84 | 139 ± 84 | 127 ± 106 | 96 ± 76 | 86 ± 65 | 172 ± 112 | 137 ± 81 | 125 ± 73 |
| Total meat (g/d) | 89 ± 61 | 118 ± 59 | 166 ± 66 | 107 ± 68 | 123 ± 60 | 163 ± 67 | 83 ± 83 | 117 ± 52 | 153 ± 60 |
| Coffee (cups)[6] | 0.9 ± 1.4 | 1.3 ± 1.6 | 1.6 ± 1.7 | 1.9 ± 2.0 | 2.3 ± 2.0 | 2.4 ± 2.1 | 1.2 ± 1.5 | 1.3 ± 1.6 | 1.3 ± 1.7 |
| Alcohol (g) | 8.6 ± 13.1 | 11 ± 15 | 13.7 ± 18 | 5.5 ± 9.7 | 6.6 ± 11 | 6.3 ± 11 | 3.0 ± 5.7 | 3.1 ± 6.0 | 3.1 ± 6.3 |
| Fruit and vegetables (serving) | 6.8 ± 3.8 | 5.5 ± 2.9 | 5.6 ± 2.8 | 4.7 ± 2.5 | 3.9 ± 2.1 | 4.0 ± 2.0 | 5.6 ± 3.3 | 4.9 ± 2.8 | 5.2 ± 2.7 |
| Vitamin C (mg)[7] | 572 ± 580 | 407 ± 447 | 332 ± 360 | 467 ± 766 | 301 ± 495 | 250 ± 428 | 345 ± 438 | 238 ± 284 | 208 ± 230 |
| Vitamin E (mg)[7] | 70 ± 115 | 48 ± 89 | 38 ± 71 | 59 ± 135 | 35 ± 97 | 27 ± 79 | 35 ± 81 | 23 ± 53 | 20 ± 44 |
| Folate ($\mu$g)[7] | 564 ± 332 | 473 ± 268 | 423 ± 220 | 445 ± 321 | 367 ± 275 | 329 ± 240 | 554 ± 332 | 465 ± 282 | 428 ± 254 |
| Multivitamin use (%) | 68 | 61 | 59 | 41 | 34 | 32 | 49 | 43 | 42 |

[1] All variables (except age) are age-standardized. NDMA, nitrosodimethylamine; NPYR, nitrosopyrolidine.
[2] $P < 0.001$ for linear trend across categories for all variables (in each cohort) by using generalized linear models for continuous variables, Similarly, for categorical variables, $P < 0.001$ for all variables by using chi-square tests.
[3] Mean ± SD (all such values).
[4] 1 inch = 2.54 cm.
[5] Among past and current smokers.
[6] 1 cup = 237 mL.
[7] Energy-adjusted nutrient intake from diet and vitamin supplement.

dogs were the top contributors; for NDMA, beer in the NHS I (1980) and skim milk in HPFS (1986) were the main sources; for NPYR, bacon was the main contributor. For these analyses, we observed no relation between nitrate, nitrites, NDMA, or NPYR intakes and the risk of glioma in the individual cohorts (data not shown) or when pooling the cohorts (**Table 4**).

Because antioxidants can influence the formation of nitrosamines in the stomach, the association between processed meat and glioma may be modified by dietary vitamin intakes. To address this possibility, we first examined whether vitamins C and E and FRAP, an indicator of total antioxidant capacity, were related to risk of glioma overall. No associations were noted for these exposures in all 3 cohorts; pooled results are shown in **Table 5**. Furthermore, no interactions were observed between intakes of total processed meat and vitamins C and E and FRAP in a comparison of high meat and low antioxidant intakes with low meat and high antioxidant intakes (data not shown; all $P$ values $>0.3$).

We observed no association with total meat, red meat, or processed meats when restricting the analyses to include only glioblastomas, which may be etiologically different from other gliomas. Furthermore, stratified analyses by age ($<56$ and $\geq 56$ y) were similar to the overall findings.

## DISCUSSION

In this study, we observed no association between meat or processed meat and risk of adult glioma. Furthermore, intake of nitrates and nitrites, which increase endogenous formation of nitrosamines, and intake of 2 preformed nitrosamines, were not related to glioma risk. Finally, there was no indication that individuals who eat processed meats but have a low antioxidant intake have a higher risk of glioma than do those who do not eat processed meats and have a high antioxidant intake.

With the exception of one cohort study, all studies to date have been case-control studies. In the cohort study, a detailed FFQ was used but only 21 cases of gliomas were identified after 6 y of follow-up (8). In this study, a relative risk of 2.3 was reported for intake of any pork products (including sausage, bacon, and ham) compared with never, but the relative risk was statistically unstable given the low case numbers. Of the 4 largest case-control studies (>200 gliomas in diet analyses), which included some assessment of meat intake (51–54), 2 studies reported statistically significant 2- to 3-fold elevations in the risk of glioma for a high intake of cured meat or bacon compared with a low intake (51, 54). However, the excess risks were only observed among men and, in one study, reported relative risks were for high intake of cured meat combined with low fruit and vegetable intake

**TABLE 2**
Total meat, red meat, and total processed meat intakes and the risk of glioma in the Health Professionals Follow-Up Study (HPFS; 1986–2004), Nurses' Health Study I (NHS I; 1980–2004), and NHS II (1991–2005)

| | Quintile of intake | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | *P* for trend[1] |
| Total meat[2] | | | | | | |
| Cases | 82 | 66 | 55 | 68 | 64 | |
| Person-years | 810,691 | 826,958 | 835,781 | 835,382 | 792,300 | |
| RR (95% CI)[3] | 1.0 | 0.71 (0.51, 0.99) | 0.66 (0.43, 1.01) | 0.88 (0.63, 1.24) | 0.81 (0.55, 1.19) | 0.65 |
| Red meat[2] | | | | | | |
| Cases | 76 | 68 | 66 | 62 | 63 | |
| Person-years | 806,694 | 833,135 | 834,460 | 831,669 | 794,937 | |
| RR (95% CI)[3] | 1.0 | 1.12 (0.81, 1.54) | 0.96 (0.68, 1.36) | 0.93 (0.64, 1.34) | 1.09 (0.62, 1.93) | 0.57 |
| Total processed meat[2] | | | | | | |
| Cases | 46 | 69 | 85 | 70 | 65 | |
| Person-years | 545,587 | 831,353 | 929,827 | 903,604 | 890,740 | |
| RR (95% CI)[3] | 1.0 | 1.11 (0.75, 1.63) | 1.14 (0.77, 1.69) | 1.17 (0.79, 1.73) | 0.92 (0.48, 1.77) | 0.99 |

[1] Based on the median value of each intake category and modeling these as continuous variables in a Cox proportional hazards model.
[2] Total meat consists of all meats except fish; red meat consists of total meat less chicken and turkey; total processed meat consists of processed meat items (eg, salami and sausage), bacon, and hot dogs. Cutoffs for quintiles were different for each cohort and are based on cumulative updated averages (g/d) over the follow-up periods: total meat (HPFS: 75, 102, 130, and 166; NHS I: 80, 119, 133, and 161; NHS II: 83, 110, 135, and 171), red meat (HPFS: 29, 51, 77, and 111; NHS I: 29, 43, 60, and 79; NHS II: 34, 52, 70, and 102), and total processed meats (HPFS: 1.8, 4.4, 7.6, and 13.9; NHS I: 1.3, 3.9, 7.1, and 12.4; NHS II: 2.1, 4.7, 7.8, and 13.2).
[3] Rate ratios (RRs) and 95% CIs from Cox proportional hazards models were adjusted for age and caloric intake (quintiles). Results were obtained from pooling the $\beta$ coefficient and SE estimates by using the DerSimonian and Laird random-effects model; no significant evidence of heterogeneity by cohort was observed ($\alpha = 0.05$).

(54). Of the 2 larger studies reporting no association for meat, it was not clear how meat intake was assessed in one study (52), and, in the second study, 76% of the data were obtained from proxy respondents (53). Among the smaller case-control studies, elevated risks have been reported for high consumption of bacon (55, 56) and meat and processed pork (57), but no associations were observed in other studies (58–62).

Vitamins C and E inhibit nitrosation reactions in vivo, and intake of these vitamins can reduce the endogenous formation of NOC in the stomach (63). Epidemiologic studies have shown that consumption of vitamin C reduces the risk of gastric cancer (64), a tumor for which NOC may be a risk factor (65). To date, most epidemiologic studies of brain tumors have had limited dietary assessments and few questions that explored the relation between vitamin intakes and the risk of glioma. Of the 9 case-control studies with data on vitamin C intake from dietary sources and/or supplements, 2 studies reported statistically significant inverse associations with vitamin C supplement use (52, 58). In a third study, a relative risk of 0.2 was observed for ever use of vitamin C supplements, but this association was not statistically significant and vitamin C intake from foods was not related to risk (55). Vitamin C intake alone was not related to risk in another study, but, when combined with cured food intake, an interaction was observed such that men with a high cured meat intake and a low intake of foods rich in vitamin C had a 2-fold increase in risk compared with those with a low cured meat intake and a high

**TABLE 3**
Bacon and hot dog intakes and the risk of glioma in the Health Professionals Follow-Up Study (HPFS; 1986–2004), Nurses' Health Study I (NHS I; 1980–2004), and NHS II (1991–2005)

| | Categories of intake | | | | |
|---|---|---|---|---|---|
| | 0 | 1–3 servings/mo | 1 serving/wk | >1 serving/wk | *P* for trend[1] |
| Bacon | | | | | |
| Cases | 118 | 111 | 61 | 45 | |
| Person-years | 1,427,325 | 1,409,855 | 839,244 | 424,689 | |
| RR (95% CI)[2] | 1.0 | 1.02 (0.79, 1.33) | 0.82 (0.58, 1.16) | 1.02 (0.72, 1.46) | 0.51 |
| Hot dogs | | | | | |
| Cases | 79 | 157 | 73 | 26 | |
| Person-years | 1,153,413 | 1,725,418 | 968,318 | 253,963 | |
| RR (95% CI)[2] | 1.0 | 1.23 (0.93, 1.63) | 1.17 (0.83, 1.65) | 1.13 (0.70, 1.82) | 0.73 |

[1] Based on the median value of each intake category and modeling these as continuous variables in a Cox proportional hazards model.
[2] Rate ratios (RRs) and 95% CIs from Cox proportional hazards models were adjusted for age and caloric intake (quintiles). Results were obtained from pooling the $\beta$ coefficient and SE estimates by using the DerSimonian and Laird random-effects model; no significant evidence of heterogeneity by cohort was observed ($\alpha = 0.05$).

**TABLE 4**
Nitrate, nitrite, nitrosodimethylamine (NDMA), and nitrosopyrolidine (NPYR) intakes and the risk of glioma in the Health Professionals Follow-Up Study (HPFS; 1986–2004), Nurses' Health Study I (NHS I; 1980–2004), and NHS II (1991–2005)

| | Quintile of intake | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | *P* for trend[1] |
| Nitrate[2] | | | | | | |
| Cases | 67 | 74 | 60 | 59 | 75 | |
| Person-years | 815,155 | 833,168 | 811,541 | 822,304 | 818,945 | |
| RR (95% CI)[3] | 1.0 | 1.06 (0.76, 1.48) | 0.84 (0.57, 1.22) | 0.95 (0.46, 1.98) | 1.02 (0.66, 1.58) | 0.81 |
| Nitrite[2] | | | | | | |
| Cases | 55 | 65 | 71 | 69 | 75 | |
| Person-years | 812,763 | 812,974 | 844,064 | 810,417 | 820,895 | |
| RR (95% CI)[3] | 1.0 | 1.11 (0.72, 1.71) | 1.20 (0.84, 1.71) | 1.14 (0.73, 1.78) | 1.26 (0.89, 1.79) | 0.23 |
| NDMA[2] | | | | | | |
| Cases | 69 | 80 | 59 | 67 | 60 | |
| Person-years | 794,817 | 1,012,119 | 672,847 | 888,972 | 732,359 | |
| RR (95% CI)[3] | 1.0 | 0.95 (0.68, 1.33) | 0.91 (0.64, 1.30) | 0.94 (0.66, 1.32) | 0.88 (0.57, 1.36) | 0.73 |
| NPYR[4] | | | | | | |
| Cases | 193 | 58 | 84 | | | |
| Person-years | 2,244,720 | 968,505 | 887,888 | | | |
| RR (95% CI)[3] | 1.0 | 0.81 (0.52, 1.20) | 0.81 (0.62, 1.05) | | | 0.93 |

[1] Based on the median value of each intake category and modeling these as continuous variables in a Cox proportional hazards model.
[2] Cutoffs for quintiles were different for each cohort and are based on baseline values: nitrate (HPFS: 87, 120, 155, and 205; NHS I: 43, 56, 87, and 145; NHS II: 78, 108, 141, and 190), nitrite (HPFS: 1.4, 1.6, 1.8, and 2.0; NHS I: 1.1, 1.3, 1.5, and 1.7; NHS II: 1.7, 1.9, 2.1, and 2.4), and NDMA (HPFS: 0.04, 0.05, 0.07, and 0.09; NHS I: 0.02, 0.04, 0.05, and 0.09; NHS II: 0.04, 0.05, 0.06, and 0.08).
[3] Rate ratios (RRs) and 95% CIs from Cox proportional hazards models were adjusted for age and caloric intake (quintiles). Results were obtained from pooling the $\beta$ coefficient and SE estimates by using the DerSimonian and Laird random-effects model; no significant evidence of heterogeneity by cohort was observed ($\alpha = 0.05$).
[4] Because of the limited range of intakes, it was not possible to create quintiles. Cutoffs are for the following tertiles: HPFS (0.01 and 0.03), NHS I (0.01 and 0.02), and NHS II (0.01 and 0.02).

intake of foods rich in vitamin C (54). The findings were similar but weaker among women (54).

The strengths of our study included its relatively large sample size, prospective design, detailed and updated information on different types of meats, and estimation of intake of nitrate, nitrite, and 2 common nitrosamines. The prospective design precluded recall bias, and selection bias was minimized by the very high rate of follow-up over a long period of time. As with any observational study on diet, measurement error is inevitable and may explain the lack of associations in the current study;

**TABLE 5**
Total dietary vitamins C and E, ferric-reducing ability of plasma (FRAP), and the risk of glioma in the Health Professionals Follow-Up Study (HPFS; 1986–2004), the Nurses' Health Study I (NHS I; 1980–2004), and NHS II (1991–2005)

| | Quintile of intake | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | *P* for trend[1] |
| Vitamin C (mg/d)[2] | | | | | | |
| Cases | 64 | 54 | 77 | 76 | 64 | |
| Person-years | 809,330 | 828,618 | 824,802 | 828,020 | 810,776 | |
| RR (95% CI)[3] | 1.0 | 0.77 (0.54, 1.12) | 1.09 (0.78, 1.53) | 1.05 (0.75, 1.47) | 0.88 (0.62, 1.26) | 0.67 |
| Vitamin E (mg/d)[2] | | | | | | |
| Cases | 62 | 60 | 79 | 63 | 71 | |
| Person-years | 809,448 | 818,459 | 820,562 | 843,170 | 809,910 | |
| RR (95% CI)[3] | 1.0 | 0.93 (0.65, 1.34) | 1.19 (0.84, 1.67) | 0.91 (0.58, 1.42) | 0.98 (0.67, 1.43) | 0.72 |
| FRAP (mmol/d)[2] | | | | | | |
| Cases | 66 | 80 | 56 | 66 | 67 | |
| Person-years | 805,989 | 824,369 | 831,714 | 830,220 | 809,256 | |
| RR (95% CI)[3] | 1.0 | 1.08 (0.71, 1.64) | 0.76 (0.53, 1.09) | 0.90 (0.63, 1.27) | 0.90 (0.64, 1.28) | 0.35 |

[1] Based on the median value of each intake category and modeling these as continuous variables in a Cox proportional hazards model.
[2] Cutoffs for quintiles were different for each cohort and are based on cumulative updated averages over the follow-up periods: vitamin C (HPFS: 155, 226, 364, and 696; NHS I: 138, 192, 279, and 500; NHS II: 119, 164, 233, and 428), vitamin E (HPFS: 11, 19, 64, and 164; NHS I: 9, 18, 53, and 160; NHS II: 9, 14, 26, and 117), and FRAP (HPFS: 9, 12, 14.5, and 19; NHS I: 9, 11, 13.5, and 17; NHS II: 7, 10, 12, and 15).
[3] Rate ratios (RRs) and 95% CIs from Cox proportional hazards models were adjusted for age and caloric intake (quintiles). Results were obtained from pooling the $\beta$ coefficient and SE estimates by using the DerSimonian and Laird random-effects model; no significant evidence of heterogeneity by cohort was observed ($\alpha = 0.05$).

however, we previously showed that dietary intake based on FFQs is well-correlated with food records in these cohorts, including for meat intake, and have reported associations with meat intake (including bacon) and cancer in these cohorts (66, 67). The repeated dietary measurements in these cohorts are important to account for changes in diet over long follow-up periods and to reduce measurement error; the analyses using the multiple dietary assessments did not alter our results. Another possibility was that the range of intakes for the different foods was not sufficiently large to detect an association; for example, we could not exclude the possibility that an association existed with meat intakes higher than those observed in these populations.

In these 3 cohort studies, we found no indication that total meat, total processed meat, nitrate, nitrite, or nitrosamine intakes were associated with risk of glioma. Similarly, we observed no relation with common antioxidants and risk of glioma or any effect modification between the 2 dietary exposures.

We thank Walter Willett for his valuable advice and Laura Sampson and Lauren Dougherty for creating the nitrite and nitrosamine database.

The authors' responsibilities were as follows—DSM: contributed to the statistical analysis, interpretation of findings, and writing of the report; EG and DJH: contributed to data collection and funding; and CNH and TB: contributed to the interpretation and editing of the manuscript. None of the authors had any conflicts of interest.

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