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An international case-control study of maternal diet during pregnancy and childhood brain tumor risk: a histology-specific analysis by food group

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Abstract

PURPOSE—Maternal dietary data from an international collaborative case-control study on childhood brain tumors were used to evaluate associations between histology-specific risk and consumption of specific food groups during pregnancy.

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DEDICATION

We dedicate this manuscript to our co-author and colleague Dr. Geoffrey Howe who died August 31, 2006 at the age of 63. Geoff was an outstanding epidemiologist who made internationally recognized contributions to the fields of cancer etiology and prevention and radiation effects, a field in which he was one of the world's foremost epidemiologists.

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

During the last few years Geoff worked closely with those of us who did the analysis of the dietary data and in numerous conference calls guided us (MBT, JMP, SP-M) in our discussion of issues related to statistical approaches and presentation of results. His collaboration in the preparation of this manuscript was invaluable.

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

Susan Preston-Martin

Mary Beth Terry

Janice M. Pogoda and all the collaborators on the IARC-coordinated case control studies of primary brain tumors in adults and children

METHODS—Nine study centers from seven countries contributed 1,218 cases and 2,223 controls. Most cases were diagnosed between 1982 and 1992 and ranged in age from 0 to 19 years. Dietary consumption was measured as average g/day.

RESULTS—Foods generally associated with increased risk were cured meats, eggs/dairy, and oil products; foods generally associated with decreased risk were yellow-orange vegetables, fresh fish, and grains. The cured meat association was specific to astrocytomas (odds ratio (OR) range=1.8–2.5 across astrocytoma subtypes for 4^{th} vs. 1^{st} quartile of consumption, p trends ≤ 0.03) and ependymomas (OR=2.0, 95% confidence interval (CI)=.4–2.9 for 4^{th} vs. 1^{st} quartile; p trend=0.03) and was similar in magnitude to previously reported ORs relating maternal cured meat consumption to increased astroglial risk. Other histology-specific associations were decreased risk of anaplastic astrocytomas from cruciferous vegetables (OR=0.4, CI=0.3–0.7 for 4^{th} vs. 1^{st} quartile; p trend < 0.0001), decreased risk of astroglial tumors from fresh fish (OR=0.6, CI=0.5–0.9 for 4^{th} vs. 1^{st} quartile; p trend=0.008), and increased risk of medulloblastoma from oil products (OR=1.5, CI=1.0–2.2 for 4^{th} vs. 1^{st} quartile; p trend=0.005).

CONCLUSIONS—These results suggest the need for dietary analysis not only by brain tumor histology, but also by specific foods within a broad food group.

Keywords

childhood neoplasms; brain tumors; diet; N-nitroso compounds; cured meat products; vegetables

INTRODUCTION

Brain tumors are the second most common neoplasm in children and have a 5-year survival rate of 67% (1). Incidence of childhood brain tumors has risen over the past three decades (2–5), partly at least due to improved diagnostics, yet little is known about their etiology (6). The role of diet – both as a risk and as a protective factor – has been investigated in several past studies. Of particular interest has been the mother's diet during pregnancy. Fetal brain cells rapidly divide during pregnancy and are highly sensitive to neoplastic changes (7), possibly because fetal brain tissue lacks alkyltransferase that repairs DNA adducts (8–10). Thus, transplacental exposure to various dietary components has been hypothesized as having an important role in brain tumor risk.

Among the most extensively studied hypotheses over the past two decades is that maternal dietary intake of N-nitroso compounds (NOC) and NOC precursors during pregnancy increases brain tumor risk in offspring. The origin of this hypothesis was the observation that a major subgroup of NOC, *N*-nitrosamides, induced brain tumors in rodent and monkey offspring after transplacental exposure via the pregnant animal's diet (11–14). Dietary exposure to *N*-nitrosamide precursors such as sodium nitrite, amines, and amides can result in endogenous formation of *N*-nitrosamides, specifically, *N*-nitrosoureas, in the acidic environment of the mammalian stomach.

In pregnant women, fetal NOC exposure may occur transplacentally (15) and may specifically target the brain due to the demonstrated organ specificity of *N*-nitrosamides (16). Cured meats are a major source of dietary NOC (17). Amines or amides in meat can be nitrosated by curing, smoking, and/or drying processes used to prevent oxidation of fatty acids in food. Nitrite in cured meats also becomes available to combine in the gut with amines and amides derived from other foods and drugs. Although vegetables contain nitrate that can be reduced to nitrite by bacteria in the saliva and can act as a nitrosating agent *in vivo* in the stomach, only a small percentage of ingested nitrate is reduced to nitrite in this way (18). Further, vegetables contain nitrosation-inhibiting antioxidants such as vitamins C and E and are generally considered more likely to be nitrosation inhibitors rather than NOC precursors (16).

This paper presents a pooled analysis of data from nine studies in seven countries that participated in the International Collaborative Study of Childhood Brain Tumors and is a companion to a similar paper from the International Collaborative Study of Adult Brain Tumors (19). Our goals for these parallel analyses were to investigate cured meat, fruit/vegetable, and other dietary associations with brain tumor risk with the largest number of cases, to date, ever studied epidemiologically. We were able to explore whether these associations, some of which have never been studied by histology, were specific to certain histologic types (because of the large number of cases) and whether there were common associations for childhood and adult brain tumors. Differences in results between the childhood and adult studies may suggest differences in importance of exposure periods; e.g., foods that increased risk in childhood but not adult brain tumors may suggest that prenatal exposure is most critical for that particular food. Six of the participating centers have previously published results from diet analyses for their particular center (20–23).

METHODS

Selection of Cases and Controls

The study design has been described in detail elsewhere (24). Data were pooled from case-control studies of risk factors for pediatric brain tumors from nine study centers in seven countries: Sydney, Australia; Winnipeg, Canada; Paris, France; Tel-Hashomer, Israel; Milan, Italy; Valencia, Spain; and Los Angeles, San Francisco, and Seattle, USA. While response rates were unavailable for some study centers (Winnipeg, Milan, and Valencia), 75% of eligible cases and 71% of eligible controls participated based on centers for which these data were available. A total of 1,218 cases and 2,223 controls were included. Years of diagnosis among cases varied by study center and ranged from 1976 to 1992; most were diagnosed between 1982 and 1992 (Table 1). Diagnosis age ranged from birth to 19 years, with some variation in the upper age by study center. Controls were frequency matched to cases in all US centers and in Paris; otherwise they were individually matched. Matching variables were region of residence, age, sex, and, at all centers except Sydney and Los Angeles, geographic area within the defined region where cases resided. For each control, a “reference age” and “reference date” were defined as either the age and date when the control reached the diagnosis age of a similar case (US centers) or the age of the control and date at the time of study selection (all other centers). Further details of control selection and other study design features at each of the participating centers are available from earlier reports (20–23;25;26).

Data Collection

Data collection at all nine study centers was performed according to a common protocol and was coordinated by the International Agency for Research on Cancer (IARC) in Lyon, France. A standardized study questionnaire asked mothers about diet and several other exposures she may have had during the “index” pregnancy, i.e., pregnancy with the study participant. For each food queried, mothers were asked about their consumption during the past year and during the index pregnancy using detailed dietary recall methods and abstract food models to gauge portion size (27–30). In general, the diet questionnaire focused on foods high in nitrate and/or nitrite and on foods containing nitrosation inhibitors such as vitamins C and E. Specific foods queried varied by study center because of regional differences in diet and due to the ability of some study groups to conduct more detailed dietary intake assessments (Table 1); the version used for the US centers is available online (31). Interviews were conducted from February 1986 through June 1995.

Data Analysis

Foods were analyzed in the following groups and subsets of groups: all fruit, citrus fruit, all vegetables, yellow-orange vegetables, cruciferous vegetables, leafy green vegetables, grains,

all meat, cured meat, non-cured meat, all fish, smoked/pickled fish, fresh fish, eggs/dairy, eggs only, cheese only, oil products, alcohol, and caffeine. Food subgroups were chosen based on food items that were on the standardized diet questionnaire. Subsets of food groups did not necessarily represent the full complement of food groups; e.g., other fruit types besides citrus were included in "all fruit." Consumption was measured as average g/day, with g/serving for each food estimated by each study center individually. Separate series of analyses that adjusted for total dietary intake were also performed by regressing average g/day on total dietary intake and using the residual value as the exposure variable. For this purpose, total dietary intake was estimated as total intake of all foods queried. The primary analysis consisted of participants of all ages. A secondary analysis consisted of participants less than 6 years old, and differences from the overall analysis in this younger age group are emphasized in Results.

Quartiles of exposure were used for categorical analyses and were defined among all respondents by study center. For foods with less than 25% consumption, the lowest exposure level was defined as non-consumers and three levels of exposure were defined by the tertiles of exposure among consumers. Dose-response was evaluated by testing category of exposure as a continuous variable and by examining odds ratios across categories for a trend effect. Maximum likelihood estimates of odds ratios (ORs) and 95% confidence intervals (CIs) were derived using both conditional and unconditional logistic regression.(32) For conditional analyses, matched sets were defined by study center, sex, and age group (0–1, 2–3, 4–5, 6–8, 9–11, 12–14, 15–19) for centers that frequency matched and by individual matching for all other centers. Unconditional analyses were stratified by study center, sex, age group and, for Seattle and Winnipeg, geographic subregion. For the other centers that matched on subregion (San Francisco, Valencia, Milan, and Israel), there were too many regional levels to allow for adjustment in unconditional analyses. Unconditional analyses were done using both all participants and only those participants included in conditional analyses (which excluded three cases and 23 controls). Estimates were similar using conditional and unconditional methods; thus, results from unconditional analyses using all subjects are reported. Generalized estimating equations were ultimately used to derive unconditional risk estimates and confidence intervals to account for correlation within study centers, with age and sex as covariates (33). Multivariable models were used to evaluate simultaneous effects of food groups when univariable trends were significant in at least one histological group; i.e., all food groups for which univariable trends were significant were included in the same model. Spearman correlation coefficients were calculated for each possible pair of food groups to evaluate collinearity. Population attributable risk (PAR) was calculated by the method of Bruzzi et al. (34); since the PAR is a monotonic transformation of the risk coefficient, its confidence limits were derived directly from the risk coefficient likelihood-based limits. Prenatal vitamin supplementation as a possible confounder of the cured meat effect was evaluated by comparing results with and without supplementation as a covariate. Cured meat effect modification by prenatal vitamin supplementation was evaluated by examining results from analyses stratified by vitamin supplementation and by testing the interaction between cured meat consumption as a continuous variable and vitamin supplementation as a binary variable. Data on vitamin supplementation were readily available from a previously published analysis {Preston-Martin, 1998 8/id}. Study heterogeneity was not formally tested due to the sheer number of tests that would have been required (thereby increasing type 1 error); however, heterogeneity was evaluated for certain food groups of interest. Statistical analyses were performed using SAS v. 9.00 (SAS Institute, Inc., Cary, NC) and Epicure v. 2.11 (Hirosoft International Corp., Seattle, WA). No adjustments for multiple tests were made; all tests were performed at the 0.05 significance level.

For histology-specific analyses, two major morphologic groups were defined: astroglial (9380–9382, 9384, 9400–9421, 9424–9442) and primitive neural ectodermal tumors (PNET) (9470–9473, 9501) (35). Morphological subgroups were: pilocytic astrocytoma (9421), anaplastic

astrocytoma (9401, 9411), other astrocytoma (9400, 9410, 9420), malignant glioma (9380), glioblastoma (9440, 9442), medulloblastoma (9470, 9471), PNET (9473), ependymoma (9391–9394), and oligodendroglioma (9450, 9451). Histologic classifications were done by the diagnosing pathologist at each study center. Only histologies with at least 50 cases were considered in histology-specific analyses. For analyses within each histology, all controls were used as the comparison group.

RESULTS

Distributions of cases and controls by study center are shown in Table 1. The number of cases by study center ranged from 45 (Winnipeg) to 304 (Los Angeles). Also shown in Table 1 is the number of foods per food group queried by each study center. A complete listing of specific foods queried by each center is available online (31).

The majority (51%) of tumors were astroglial, with a large proportion of those (32%) being astrocytomas. Twenty-one percent of all tumors were PNET, most commonly medulloblastomas (75%). Among all other tumors, ependymomas were relatively common (32% of all other tumors, or 9% of all brain tumors).

Multivariable risk estimates and tests for trend for food groups that were univariably significant in at least one histological subgroup are shown in Table 2 for all tumors combined and for both major tumor types (astroglial and PNET). Table 3 summarizes key findings by selected food group for seven tumor subtypes (pilocytic, anaplastic, and all other astrocytomas; malignant gliomas; medulloblastomas; PNET ICD-O 9473; and ependymomas). The lengthy complete table of findings from multivariable analyses of the seven subtypes for all food groups is available online (31). Tables showing univariable risk estimates for all food groups and for the seven subtypes are also available online (31). Although we emphasize the multivariable results, univariable estimates are also presented for comparability with previous research which typically reported only univariable findings.

The strongest correlation between food groups was 0.44, for leafy-green and cruciferous vegetables. There was no relationship between intake of all queried foods combined and childhood brain tumor risk; thus, all reported risk estimates are unadjusted for intake of all foods combined. Food groups that were univariably significant in at least one histological subgroup (and therefore used in multivariable analyses) were leafy green vegetables, yellow-orange vegetables, cruciferous vegetables, cured meat, non-cured meat, fresh fish, eggs/dairy, grains, caffeine, and oil products; all fruit was also included as it was univariably significant among tumors that were neither astroglial nor PNET (data not shown). Results presented in the following text are from multivariable analyses unless otherwise noted, and reported ORs and CIs are for the comparison of the highest to the lowest level of consumption.

Vegetables

Yellow-orange vegetables were related to decreased risk for all tumors combined (OR = 0.8, CI = 0.6, 1.0; p trend = 0.04; Table 2), and in younger children (< 6 years) this was the only association that remained significant multivariably for all tumors combined (data not shown). As shown in Table 3 and in the full table of tumor subtype multivariable results (31), the yellow-orange vegetable finding was strongest for pilocytic astrocytomas (OR = 0.5, CI = 0.4, 0.6; p trend = 0.0004) and anaplastic astrocytomas (OR = 0.6, CI = 0.4, 1.0; p trend = 0.03). A significant decreasing trend was also observed for PNETs (p = 0.0002, Table 2), including among younger children, but descriptively the relationship was not as compelling as those observed for the astrocytoma subtypes (31). Univariably, cruciferous vegetables were significantly related to decreased risk of all tumors combined (OR = 0.8, CI = 0.05–1.1, p trend = 0.03) but multivariably the association was maintained only for anaplastic astrocytomas (OR

= 0.4, CI = 0.3–0.7, p trend < 0.0001; Table 3). Neither yellow-orange nor cruciferous vegetables were significant for all astrocytomas combined (Table 2).

Cured Meats

Cured meats were associated with increased risk for all tumors combined but particularly for astroglial tumors (OR = 1.5, CI = 1.1–2.1, p trend = 0.03; Table 2). Center-specific univariable ORs associated with the highest level of cured meat intake and risk of astroglial tumor are shown in Figure 1. Risk estimates were increased for all centers except Valencia and were significantly increased for Sydney, Seattle, and all centers combined; in addition, as previously reported (20), risk from cured meats was significantly increased among all US centers combined (OR = 1.9, CI = 1.4–1.6, p trend = 0.003). Among all centers combined, the PAR for astroglial tumors from the highest exposure level of cured meats was 10% (CI = 6%, 13%). As shown in Table 3, the cured meat association was significant for all three astrocytoma subgroups (OR = 2.5, CI = 1.1–5.8, p trend = 0.03 for pilocytic; OR = 2.1, CI = 1.1–4.3, p trend = 0.004 for anaplastic; OR = 1.8, CI = 1.2–2.7, p trend = 0.008 for all other astrocytomas). There was no evidence of confounding or effect modification by prenatal vitamin supplementation (data not shown).

Fish

Fresh fish consumption at the highest level was associated with decreased risk for all tumors combined and particularly for astroglial tumors (OR = 0.6, CI = 0.5–0.9, p trend = 0.005; Table 2), including among younger children (data not shown); however, no trend was descriptively apparent (i.e., only the highest level of exposure had OR < 1) and results within tumor subtypes were mixed (Table 3). For example, the 4^{th} quartile OR (CI) was 0.5 (0.3, 0.6) for malignant gliomas but was 1.6 (1.1, 24) for anaplastic astrocytomas. Smoked/pickled fish was unrelated to brain tumor risk.

Eggs/Dairy

Egg/dairy products were associated with increased risk of all tumors combined as well as within the astroglial and PNET types (Table 2). Within astroglial tumors, the relationship was present for all subtypes except malignant gliomas and was strongest for pilocytic astrocytomas (OR = 2.1, CI = 1.0, 4.1, p trend = 0.02; Table 3). Eggs/dairy products were significantly related to risk univariably for PNETs but not astroglial tumors or all tumors combined (31).

Grains

Grains were related to decreased risk for all tumors combined and for astroglial tumors (Table 2), as well as for the PNET (ICD-O 9473) subtype (Table 3). Within astroglial tumors, the reduced risk was limited to pilocytic astrocytomas (OR = 0.7, CI = 0.6–1.0, p trend = 0.002; Table 3) and malignant gliomas (OR = 0.3, CI = 0.1–0.6, p trend = 0.0003; Table 3). Conversely, risk associated with grains was significantly increased for medulloblastomas (OR = 1.3, CI = 1.0–1.8, p trend = 0.02; Table 3). The univariable results were significant only for malignant gliomas and medulloblastomas (31).

Oil Products

Oil products were related to increased risk of PNETs (OR = 1.4, CI = 1.0–1.9, p trend = 0.008; Table 2), and this association was borderline significant among younger subjects as well (data not shown). Increased risk appeared limited to the medulloblastoma subtype (OR = 1.5, CI = 1.0–2.2, p trend = 0.005; Table 3).

Other Food Groups

There were no significant associations between brain tumor risk and consumption of all fruit (i.e., including the citrus subgroup), leafy green vegetables, smoked/pickled fish, alcohol, or caffeine.

DISCUSSION

Maternal diet during pregnancy was significantly related in multivariable models to risk of childhood brain tumor for a subset of food groups that we analyzed: cured meats, eggs/dairy, and oil products were associated with increased risk, while yellow-orange and cruciferous vegetables, fresh fish, and grains were associated with decreased risk. Food groups that showed no associations with brain tumor risk were all fruit (i.e., including the citrus subgroup), leafy green vegetables, smoked/pickled fish, alcohol, and caffeine. Our analyses by histological tumor type suggested certain food groups that were more strongly associated with specific tumor types than others: cured meats with astrocytomas (increased risk), cruciferous vegetables with anaplastic astrocytomas (decreased risk), yellow-orange vegetables with anaplastic and pilocytic astrocytomas as well as PNETs (decreased risk), fresh fish with astroglial tumors (decreased risk), and oil products with medulloblastomas (increased risk).

Comparisons to Previous Studies

One of the two major subgroups of NOC, *N*-nitrosamides, have been hypothesized as carcinogens specific to the central nervous system, based on results from animal studies (16). Cured meats consumed by the mother during pregnancy are the most likely dietary source of transplacental NOC exposure to the fetus. The first report of an association between maternal consumption of cured meats during pregnancy and childhood brain tumor risk was from a Los Angeles County case-control study published in 1982 (36). Since then, 10 other case-control studies, four that are part of the international study presented in this report, have examined the association between childhood brain tumors and cured meat and/or nitrate/nitrite consumption (20–23;37–42). Of the six studies not part of the international study, three considered all histologies of brain tumor combined (36;40;41), two considered only astroglial tumors (37; 39), and two considered only PNETs (38;42). In general, the four studies not restricted to PNETs observed statistically significant and, in some studies dose-related, increases in childhood brain tumor risk for high maternal consumption of cured meats, with ORs ranging from 1.7 to 6.0; the two studies that analyzed only PNETs observed no associations between cured meats and brain tumor risk. Thus, the international study supports the findings from earlier studies that maternal cured meat consumption during pregnancy may increase risk of childhood brain tumors and further supports the additional hypothesis that increased risk may be specific to astrocytomas (38;39). It is unclear why risk would be specific to this histology, but this finding may be an important clue in the etiology of astroglial tumors as well as types that appear unrelated to cured meats.

Studies that have analyzed maternal consumption of nitrate and nitrite from all foods combined have observed no (20;21;39) or protective (22;38) associations with childhood brain tumor risk. The US centers (from the international collaborative study) previously reported a clear positive association between maternal nitrite consumption from cured meats and childhood brain tumor risk but no association for nitrite from vegetables or from all foods combined (20). This suggests that brain tumor risk may be specific to NOC ingested without nitrosation-inhibiting antioxidants, such as those contained in vegetables. In support of this, we found no evidence in the collaborative study of an interactive effect between cured meat consumption and prenatal vitamin supplementation; i.e., the timing between NOC and vitamin ingestion may be more important than the actual exposure itself.

In our vegetable analyses, we found that decreased risk was associated only with cruciferous and yellow-orange vegetables, and that cruciferous vegetables were particularly associated with anaplastic astrocytomas while a yellow-orange vegetable effect related to both anaplastic and pilocytic astrocytomas. Four previous studies have analyzed the effect of maternal vegetable intake on childhood brain tumor risk. The first of these was the 1982 Los Angeles County study that considered all tumor types combined and analyzed only high-nitrate vegetables (spinach, collards, eggplant, beets, and radishes) (36), and no risk associations were observed. In one of the later three studies, a significant trend of decreasing risk was associated with vegetable consumption but the effect was specific to PNETs (38). No vegetable effects were observed for either astroglials or PNETs in the remaining two studies (42;43). Notably, a nonsignificant trend of decreasing risk of medulloblastoma was associated with winter squash in one of the studies (42). Winter squash is a fruit but, like yellow-orange vegetables, is a rich source of carotenoids which have been shown to reduce risk of cancer due to their antioxidant properties when consumed as part of the diet rather than through supplementation (44). Along with anaplastic and pilocytic astrocytomas, we also observed significantly reduced risk from yellow-orange vegetables for medulloblastomas; however, the descriptive trend was not as compelling (31).

Cruciferous vegetables are rich in isothiocyanates, potent inducers of phase II enzymes, such as glutathione-S-transferases (GSTs), which protect cells from DNA damage from carcinogens (45;46). On the other hand, consumption of cruciferous vegetables also induces cytochrome P450s (CYPs), phase I enzymes involved in mutation induction. It has been shown that apiaceous vegetables, which include carrots, decreases CYP1A2 activity (47). The specificity of decreased risk from cruciferous and yellow-orange vegetables to certain brain tumor histologies may relate to the fact that different vegetable groups have different effects on phase I and phase II enzymes, and the action of these enzymes are affected by genetic markers. For example, it has been hypothesized that individuals with inherited homozygous deficiency in GSTM1 experience increased CYP1A2 activity among frequent consumers of cruciferous vegetables (48).

Significant associations between fruit and especially fruit juice consumption by the mother during pregnancy and decreased risk of PNETs has been reported previously (38;42) but for astroglial tumors this effect was reportedly only among higher-income participants (39). In our study, we observed a non-significant trend of decreasing risk of PNET associated with fruit consumption; for other tumor histologies, fruit was clearly unrelated to risk.

Very few studies have reported on effects of dietary fish on brain tumor risk. The Children's Cancer Group observed significantly decreased risk of PNET associated with "fish not smoked, pickled, or salted"(38). Although we observed a significant effect of reduced astroglial risk for fresh fish, there was not a clear dose-response relationship. To our knowledge, no previous studies have reported on the effects of maternal dietary eggs/dairy, grains, or oil products on childhood brain tumor risk. We observed reduced risk for grains and increased risk for eggs/dairy for all tumor types, and increased risk for oil products for medulloblastomas. These are interesting hypothesis-generating observations that can be further evaluated in future studies.

We found no associations between brain tumor risk and maternal consumption of alcohol or caffeine during pregnancy. This argues against report bias; i.e., mothers of cases being more likely to report foods that are generally perceived as unhealthy (such as cured meats). Most, but not all, previous studies of childhood brain tumor and maternal diet also reported no associations with alcohol or caffeine (36–39;41;49;50). For all brain tumor histologies combined, Howe observed increased risk associated with beer consumption during pregnancy (ever versus never) (30), while Schymura reported decreased risk for wine consumption (41).

Bunin reported an elevated risk for beer among PNETs and an elevated risk for the highest quartile of cola consumption among lower-income astrocytoma participants (39;43).

Study Limitations

There were limitations to our analysis that must be noted. Overall participant response rates were unavailable as some individual studies from the pooled analysis were not published previously and investigators are now retired or deceased. A general limitation for large collaborative efforts such as this is that analysis can occur long after center-specific data collection and funding have ended, making it difficult or impossible to ascertain pertinent data or information. The number of cases by study center varied, from 45 in Winnipeg to 304 in Los Angeles; thus, our findings were dominated by the larger study centers and may not accurately reflect true geographical differences. Because foods eaten vary greatly by geographic region, it was impossible to have a single dietary questionnaire that could be used by all study centers. This resulted in non-uniform ascertainment of consumption of the food groups we analyzed that may have increased measurement error and may have increased the contribution from some study centers to the overall analysis. An extreme example is that some centers were excluded from analyses of certain foods because those foods were not part of those centers' questionnaires.

The questionnaires were not validated in terms of their ability to capture true total dietary intake or consumption of the various dietary constituents of interest or of the food groups we analyzed. A similar shortened food list, used in a Canadian study and selected in the same way as for the geographic areas in our study, was shown to correlate very well with estimates based on a full diet history for seven dietary components, including nitrosamines (30). Nonetheless, the questionnaires were not specifically designed to ascertain consumption of the food groups we analyzed. For example, the most commonly eaten foods in each of the food groups were not necessarily included in the questionnaires. The result of this is likely to be underestimation of consumption and therefore increased measurement error leading to attenuated risk estimates for those food groups for which commonly eaten foods were not queried.

Another contributor to possible measurement error that is present in all case-control studies was the reliance on recall. Respondents were asked to recall their diets during their pregnancies that were in excess of 10 years in the past for some women. Although little has been reported on accuracy of pregnancy diet recall, one recent study suggested that women's recall of their diets during pregnancy was comparable to recall of past diet among adults in general (51). Further, another study showed that accuracy of diet recall did not differ by length of elapsed time (52). While it is likely that risk estimates in our study were attenuated due to inaccurate recall, the existence of differential recall in our data seems less likely due to the lack of associations we observed for foods such as alcohol and caffeine. Further, associations unique to specific histologies are unlikely to be the result of recall bias.

Correlated measurement error is of particular concern in nutritional epidemiology, where dietary data consisting of several different foods are commonly self-reported. The effects of correlated error on multivariable risk estimates are unpredictable. It has been suggested that adjustment for total intake in multivariable modeling reduces the correlation between food variables (53). We found that adjusting for total intake of foods queried (as a surrogate for total dietary intake) had little effect on risk estimates. Further, the highest pairwise correlation we observed was relatively modest (0.44). Nonetheless, our results must be interpreted in light of possible measurement error correlation that may have created spurious associations, particularly since we had to use a surrogate for total intake that has not been validated.

Because this was a hypothesis-generating as well as a hypothesis-testing analysis, the overall type 1 error rate was not controlled. Therefore, results and conclusions should be interpreted

keeping in mind that numerous statistical tests were done with outcomes that were clearly not independent. For example, for major tumor types, 18 food groups were analyzed for each of three subgroups (all tumors, astroglial tumors, and PNETs), for a total of 54 tests. If these tests were independent, we would expect two to three significant results by chance alone with a 0.05 significance level. We observed 13 significant results, but many of these were strongly correlated; thus, more than two to three significant results could reasonably occur by chance alone. For instance, because astroglials and PNETs are subsets of all tumors combined, a test of the null hypothesis for all tumors combined would be highly correlated with separate tests for astroglials and PNETs. Among astroglials and PNETs only (two disjoint groups), we observed eight significant results when one to two would be expected; but, again, some outcomes were subsets of others (e.g., citrus fruit and all fruit).

As with any epidemiological study, it is possible that any one of our findings reflect the effect of an unmeasured confounder rather than the effect of the specific food group that was analyzed; e.g., there may be an unknown environmental factor that is positively correlated with both childhood brain tumor risk and maternal consumption of cured meats. A general rule of thumb that has been substantiated is that relative risk estimates may be off by as much as a factor of two due to unmeasured correlates of disease and risk factors (54).

Comparison to Adult Companion Study

In our companion study of adult diet, there was no association between consumption of cured meats and adult brain tumor risk (19). A possible explanation for the lack of association is increased nondifferential measurement error, in that brain tumors in adults likely develop over a long time period and dietary information obtained at the time of interview may not reflect long-term patterns of intake or patterns during crucial etiologic periods. Another possible explanation is biology; e.g., it has been suggested that fetal brain tissue may be more sensitive to NOC exposure than adult brain tissue (14). Interestingly, both childhood and adult studies observed decreased risk from yellow-orange vegetables associated with astroglial tumors, strengthening the hypothesis that the association is histology-specific and suggesting that the differing results for cured meats is more biological than methodological.

Conclusions

In comparing our findings to those from previous childhood brain tumor studies, it is important to consider the potential for publication bias; i.e., that null findings may not have been published or that certain findings may have been selectively reported. The most reliable nutritional epidemiology studies are prospective, but cohort studies of maternal diet during pregnancy and risk of childhood brain tumors are not feasible, especially for subtype-specific analyses due to the low incidence of each subtype. Studies that combine all histologies may result in a case group too heterogeneous to uncover certain risk factors. Results from the international collaborative study presented here are an important contribution to the sizeable existing literature on diet and childhood brain tumor risk in that they support the previously suggested possibility of transplacental NOC exposure as a risk factor. Further, this study was large enough to explore dietary associations within tumor subtypes, thus providing hypotheses for future, more directed research. Our findings also suggest the need for dietary analysis not only by histology, but also by specific foods within a broad food group. An example of this is our analysis of vegetables, which showed that maternal consumption of vegetables in general was not associated with brain tumor risk but that consumption of cruciferous and yellow-orange vegetables appeared to reduce risk and that this effect was more apparent for certain tumor types. If the histology-specific associations we observed can be confirmed, it would strengthen the foundation on which research into the etiology of childhood brain tumors could be based.

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Abbreviations

CI	95% confidence interval
CYP	cytochrome P450
GST	glutathione-S-transferase
IARC	International Agency for Research on Cancer
NOC	N-nitroso compounds
OR	odds ratio
PAR	population attributable risk

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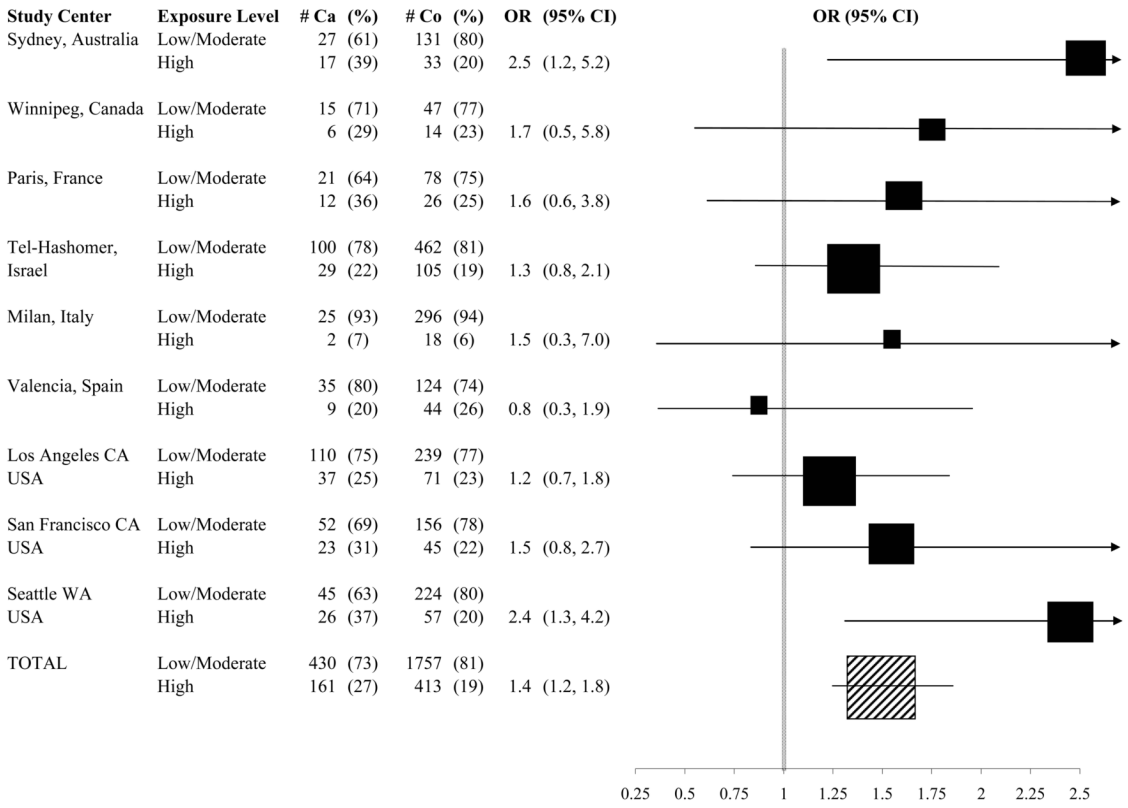

Figure 1.

Univariable odds ratios (OR) and 95% confidence intervals (CI) relating astroglial risk and "high" exposure (highest of 4 levels) to cured meats adjusted for age at diagnosis and sex, overall and by study center, international collaborative case-control study of maternal diet during pregnancy and childhood brain tumor risk. Sizes of boxes representing ORs are proportional to inverse variances of risk estimates. Lines through boxes depict 95% CIs.

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Table 1

Number of foods per food group by study center, international collaborative case-control study of maternal diet during pregnancy and childhood brain tumor.

	Australia	Canada	France	Israel	Italy	Spain	USA
	Sydney	Winnipeg	Paris	Tel-Hashomer	Milan	Valencia	LA/SF/Sea.[1]
Number of Cases	82 (7%)	45 (4%)	75 (6%)	300 (25%)	90 (7%)	86 (7%)	540 (44%)
Number of Controls	164 (7%)	83 (4%)	113 (5%)	574 (26%)	318 (14%)	170 (8%)	970 (36%)
Diagnosis Years	1985 – 1989	1980 – 1994	1984 – 1990	1976 – 1992	1984 – 1989	1983 – 1992	1984 – 1992
Food Group:[2]							
All foods analyzed	63	46	55	110	44	36	42
All vegetables	17	11	12	26	15	8	9
Cruciferous vegetables	4	3	1	3	2	1	2
Leafy green vegetables	2	2	2	1	2	1	2
Yellow-orange vegetables	2	1	1	2	1	0	1
Cured meat	8	10	4	4	4	8	6
Non-cured meat	3	2	0	4	1	1	1
Fish	4	4	3	6	2	4	2
Fresh fish	1	1	1	4	1	1	1
Smoked/pickled fish	3	3	1	2	1	2	1
Eggs/dairy	2	2	3	10	3	4	3
Cheese only	0	1	1	1	1	1	2
Eggs only	1	1	1	1	1	1	1
Grains	5	5	1	24	3	3	4
All fruit	11	4	8	20	7	4	8
Citrus fruit	3	3	4	3	4	2	4
Caffeine	3	3	3	5	3	1	3
Oil products	2	2	14	8	2	1	3
Alcohol	7	3	4	3	4	3	3

[1] Numbers (percentages) of cases from Los Angeles, San Franciso, and Seattle were 304 (25), 102 (8), and 134 (11), respectively; numbers (percentages) of controls were 315 (14), 205 (9), and 281 (13).

[2] Subsets of food groups did not necessarily represent the full complement of food groups; e.g., other fruit types besides citrus were included in “all fruit.”

Table 2

Multivariable[1] odds ratios (OR) and 95% confidence intervals (CI) for food groups, overall and by major tumor type, international collaborative case-control study of maternal diet during pregnancy and childhood brain tumor risk.

			All Tumors (N = 1203 cases) (median age at dx = 7 yrs)				Astroglials[2] (N = 621 cases) (median age at dx = 7 yrs)				PNETs[3] (N = 257 cases) (median age at dx = 6 yrs)			
Food group[4]	**Controls**		**Cases**				**Cases**				**Cases**			
Exposure level	**No.**	**(%)**	**No.**	**(%)**	**OR**	**(95% CI)**	**No.**	**(%)**	**OR**	**(95% CI)**	**No.**	**(%)**	**OR**	**(95% CI)**
Cruciferous vegetables														
1st	1195	(55)	652	(55)	1.0		309	(52)	1.0		146	(59)	1.0	
2nd	318	(15)	189	(16)	1.0	(0.9, 1.2)	109	(18)	1.2	(1.0, 1.4)	34	(14)	0.9	(0.7, 1.3)
3rd	332	(15)	175	(15)	0.9	(0.8, 1.1)	94	(16)	0.9	(0.8, 1.2)	35	(14)	0.9	(0.7, 1.4)
4th	339	(16)	159	(14)	0.9	(0.6, 1.4)	87	(15)	1.0	(0.6, 1.5)	34	(14)	1.0	(0.5, 1.7)
p trend					0.45				0.64				0.88	
Leafy-green vegetables														
1st	964	(44)	535	(46)	1.0		251	(42)	1.0		125	(50)	1.0	
2nd	405	(19)	221	(19)	0.9	(0.6, 1.5)	111	(19)	1.0	(0.7, 1.3)	46	(18)	0.9	(0.4, 1.9)
3rd	425	(19)	193	(16)	0.9	(0.6, 1.2)	112	(19)	1.0	(0.7, 1.4)	34	(14)	0.6	(0.3, 1.3)
4th	392	(18)	226	(19)	1.1	(0.9, 1.4)	123	(21)	1.2	(0.8, 1.6)	44	(18)	1.0	(0.7, 1.5)
p trend					0.60				0.45				0.71	
Yellow-orange vegetables														
1st	710	(36)	420	(40)	1.0		209	(39)	1.0		87	(38)	1.0	
2nd	426	(21)	215	(20)	0.9	(0.7, 1.1)	95	(18)	0.7	(0.5, 1.1)	59	(26)	1.2	(0.9, 1.5)
3rd	404	(20)	214	(20)	0.8	(0.7, 1.0)	121	(23)	0.9	(0.7, 1.3)	38	(17)	0.7	(0.5, 0.8)
4th	444	(22)	208	(20)	0.8	(0.6, 1.0)	111	(21)	0.8	(0.6, 1.1)	42	(19)	0.6	(0.4, 0.9)
p trend					0.04				0.24				0.0002	
Cured meat														
1st	873	(40)	375	(32)	1.0		170	(29)	1.0		87	(36)	1.0	
2nd	454	(21)	236	(20)	1.1	(0.9, 1.2)	128	(22)	1.1	(1.0, 1.3)	43	(18)	1.1	(0.8, 1.4)
3rd	430	(20)	261	(23)	1.2	(1.0, 1.5)	132	(22)	1.3	(1.0, 1.9)	59	(24)	1.1	(0.9, 1.4)
4th	413	(19)	284	(25)	1.5	(1.1, 2.1)	161	(27)	1.8	(1.2, 2.6)	52	(22)	1.2	(0.9, 1.6)
p trend					0.03				0.01				0.15	
Non-cured meat														

	All Tumors (N = 1203 cases) (median age at dx = 7 yrs)						Astroglials[2] (N = 621 cases) (median age at dx = 7 yrs)				PNETs[3] (N = 257 cases) (median age at dx = 6 yrs)			
Food group[4]	**Controls**		**Cases**				**Cases**				**Cases**			
Exposure level	**No.**	**(%)**	**No.**	**(%)**	**OR**	**(95% CI)**	**No.**	**(%)**	**OR**	**(95% CI)**	**No.**	**(%)**	**OR**	**(95% CI)**
1st	1187	(54)	652	(55)	1.0		345	(57)	1.0		137	(55)	1.0	
2nd	285	(13)	145	(12)	1.0	(0.9, 1.2)	73	(12)	1.0	(0.9, 1.1)	27	(11)	0.9	(0.6, 1.5)
3rd	274	(13)	133	(11)	1.0	(0.8, 1.2)	58	(10)	0.9	(0.6, 1.3)	34	(14)	1.2	(1.0, 1.4)
4th	437	(20)	247	(21)	1.2	(1.0, 1.3)	128	(21)	1.2	(1.0, 1.4)	49	(20)	1.0	(0.8, 1.3)
p trend						0.19				0.49				0.45
Fresh fish														
1st	654	(30)	410	(35)	1.0		219	(36)	1.0		74	(30)	1.0	
2nd	427	(20)	242	(21)	1.2	(0.9, 1.6)	115	(19)	1.1	(0.8, 1.4)	53	(21)	1.5	(1.0, 2.3)
3rd	535	(25)	289	(25)	1.0	(0.9, 1.2)	157	(26)	1.0	(0.9, 1.2)	69	(28)	1.4	(1.2, 1.7)
4th	566	(26)	237	(20)	0.7	(0.6, 0.9)	112	(19)	0.6	(0.5, 0.9)	51	(21)	0.9	(0.7, 1.3)
p trend						0.01				0.005				0.99
Eggs/dairy[5]														
1st	554	(26)	280	(24)	1.0		142	(24)	1.0		49	(20)	1.0	
2nd	556	(26)	274	(24)	1.0	(0.8, 1.3)	139	(24)	1.0	(0.7, 1.4)	55	(23)	1.3	(1.0, 1.6)
3rd	533	(25)	296	(26)	1.1	(0.8, 1.5)	151	(26)	1.2	(0.9, 1.5)	70	(29)	1.6	(1.0, 2.7)
4th	525	(24)	301	(26)	1.2	(1.0, 1.5)	154	(26)	1.3	(1.0, 1.7)	68	(28)	1.6	(1.0, 2.4)
p trend						0.04				0.01				0.049
Grains														
1st	527	(24)	309	(27)	1.0		167	(28)	1.0		53	(22)	1.0	
2nd	557	(26)	290	(25)	0.9	(0.7, 1.1)	141	(24)	0.8	(0.5, 1.1)	60	(24)	1.0	(0.7, 1.5)
3rd	561	(26)	272	(23)	0.8	(0.7, 1.0)	133	(23)	0.7	(0.5, 1.0)	63	(26)	1.1	(0.9, 1.5)
4th	526	(24)	292	(25)	0.9	(0.8, 0.9)	150	(25)	0.8	(0.7, 0.9)	69	(28)	1.1	(0.8, 1.5)
p trend						< 0.0001				< 0.0001				0.44
All fruit														
1st	515	(24)	312	(27)	1.0		149	(25)	1.0		67	(28)	1.0	
2nd	555	(26)	267	(23)	0.8	(0.6, 1.0)	145	(25)	0.9	(0.7, 1.2)	61	(25)	0.8	(0.5, 1.4)
3rd	521	(24)	301	(26)	0.9	(0.7, 1.2)	162	(28)	1.1	(0.8, 1.4)	58	(24)	0.8	(0.5, 1.5)
4th	554	(26)	266	(23)	0.8	(0.6, 1.0)	130	(22)	0.8	(0.6, 1.2)	57	(23)	0.7	(0.5, 1.1)
p trend						0.15				0.43				0.15

	All Tumors (N = 1203 cases) (median age at dx = 7 yrs)						Astroglials[2] (N = 621 cases) (median age at dx = 7 yrs)				PNETs[3] (N = 257 cases) (median age at dx = 6 yrs)			
Food group[4]	**Controls**		**Cases**				**Cases**				**Cases**			
Exposure level	**No.**	**(%)**	**No.**	**(%)**	**OR**	**(95% CI)**	**No.**	**(%)**	**OR**	**(95% CI)**	**No.**	**(%)**	**OR**	**(95% CI)**
Caffeine														
1st	587	(27)	254	(22)	1.0		133	(23)	1.0		53	(22)	1.0	
2nd	513	(24)	305	(27)	1.2	(1.0, 1.5)	149	(25)	1.1	(0.8, 1.6)	64	(27)	1.2	(0.7, 1.9)
3rd	521	(24)	312	(27)	1.3	(1.0, 1.6)	169	(29)	1.3	(1.1, 1.6)	55	(23)	1.0	(0.6, 1.8)
4th	527	(25)	278	(24)	1.1	(0.9, 1.4)	135	(23)	1.0	(0.8, 1.2)	68	(28)	1.2	(1.0, 1.5)
p trend					0.36				0.60				0.12	
Oil products														
1st	557	(26)	287	(25)	1.0		156	(26)	1.0		54	(22)	1.0	
2nd	571	(26)	297	(26)	0.9	(0.7, 1.2)	150	(25)	0.8	(0.7, 1.1)	52	(21)	0.9	(0.5, 1.6)
3rd	519	(24)	275	(24)	1.0	(0.8, 1.3)	140	(24)	1.0	(0.7, 1.3)	62	(25)	1.2	(0.8, 1.9)
4th	523	(24)	300	(26)	1.1	(0.7, 1.6)	146	(25)	0.9	(0.7, 1.3)	76	(31)	1.4	(1.0, 1.9)
p trend					0.54				0.91				0.008	

[1] Simultaneous analysis of food groups for which trends were univariably significant for at least one histological subtype. Individual vegetable subgroups rather than all vegetables combined were analyzed because all vegetables combined were not univariably significant. Fresh fish rather than all fish combined was analyzed because the effect of all fish combined was driven by the fresh fish subgroup. Dairy rather than the egg and/or cheese subgroups was analyzed because all eggs/dairy combined but not eggs or cheese was univariably significant for at least one major tumor type. All fruit combined (but not citrus fruit) was included because of a univariable significant result among tumors that were neither astroglial nor PNET. Specific food groups included differ from the adult brain tumor analysis because different food groups were univariably significant. Models for analyses of each food group included all other foods in the table plus study center, age, and sex.

[2] ICD-O 9380–9382, 9384, 9400–9421, and 9424–9442.

[3] ICD-O 9470–9473 and 9501.

[4] Subsets of food groups did not necessarily represent the full complement of food groups; e.g., other fruit types besides citrus were included in “all fruit.”

[5] Includes cheese.

Table 3

Multivariable[1] odds ratios (OR) and 95% confidence intervals (CI) for selected food groups, by tumor subtype, international collaborative case-control study of maternal diet during pregnancy and childhood brain tumor risk.

	Pilocytic Astrocytomas[2] (N=142 cases) (med dx age = 6)		Anaplastic Astrocytomas[3] (N=96 cases) (med dx age = 11)		Other Astrocytomas[4] (N=199 cases) (med dx age = 7)		Malignant Gliomas[5] (N=122 cases) (med dx age = 6)		Medullo-blastomas[6] (N=193 cases) (med dx age = 6)		PNET (ICD-O 9473) (N=64 cases) (med dx age = 5)		Ependy-momas[7] (N=104 cases) (med dx age = 4)	
Food group	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Cruciferous vegetables	1.2	(0.6, 2.6)	0.4	(0.3, 0.7)	0.8	(0.5, 1.5)	1.1	(0.6, 2.3)	0.6	(0.3, 1.3)	1.7	(0.7, 3.7)	0.8	(0.3, 2.2)
p trend		0.57		< 0.0001		0.45		0.79		0.44		0.51		0.74
Yellow-orange vegetables	0.5	(0.4, 0.6)	0.6	(0.4, 1.0)	0.7	(0.5, 1.1)	1.1	(0.9, 1.3)	0.5	(0.3, 0.8)	0.8	(0.4, 1.7)	0.7	(0.3, 1.4)
p trend		0.0004		0.03		0.21		0.18		0.0004		0.45		0.22
Cured meat	2.5	(1.1, 5.8)	2.1	(1.1, 4.3)	1.8	(1.2, 2.7)	1.9	(0.9, 3.9)	1.1	(0.9, 1.3)	1.5	(0.5, 4.8)	2.0	(1.4, 2.9)
p trend		0.03		0.004		0.008		0.13		0.43		0.38		0.03
Non-cured meat	1.1	(0.5, 2.8)	1.2	(0.3, 4.6)	1.2	(1.1, 1.3)	0.9	(0.7, 1.3)	1.0	(0.7, 1.5)	1.1	(0.6, 1.9)	1.3	(0.7, 2.2)
p trend		0.54		0.72		0.46		0.74		0.41		0.65		0.70
Fresh fish	0.7	(0.4, 1.2)	1.6	(1.1, 2.4)	0.7	(0.4, 1.0)	0.5	(0.3, 0.6)	1.0	(0.6, 1.7)	0.8	(0.5, 1.1)	0.9	(0.5, 1.5)
p trend		0.19		0.02		0.054		0.001		0.71		0.29		0.24
Eggs/dairy	2.1	(1.0, 4.1)	1.1	(0.8, 1.5)	1.4	(1.0, 1.8)	1.0	(0.4, 2.3)	1.4	(1.0, 1.9)	2.0	(0.6, 6.1)	0.8	(0.4, 1.6)
p trend		0.02		0.11		0.001		0.83		0.14		0.06		0.66
Grains	0.7	(0.6, 1.0)	1.1	(0.6, 2.1)	1.0	(0.8, 1.2)	0.3	(0.1, 0.6)	1.3	(1.0, 1.8)	0.8	(0.6, 1.0)	0.8	(0.5, 1.3)
p trend		0.002		0.76		0.22		0.0003		0.02		0.002		0.69
Oil products	0.6	(0.4, 1.0)	0.7	(0.2, 2.2)	0.9	(0.7, 1.3)	1.1	(0.6, 2.0)	1.5	(1.0, 2.2)	1.0	(0.6, 1.7)	1.1	(0.5, 2.5)
p trend		0.13		0.40		0.93		0.76		0.005		0.66		0.83

[1] Simultaneous analysis of selected food groups from those for which trends were univariably significant for at least one histological subtype. Specific food groups included differ from the adult brain tumor analysis because different food groups were univariably significant. Models for analyses of each food group included study center, age, and sex.

[2] ICD-O 9421.

[3] ICD-O 9401 and 9411.

[4] ICD-O 9400, 9410, and 9420.

[5] ICD-O 9380.

[6] ICD-O 9470 and 9471.

[7] ICD-O 9391–9394.