Maternal Supplement, Micronutrient, and Cured Meat Intake during Pregnancy and Risk of Medulloblastoma during Childhood: A Children's Oncology Group Study

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Abstract

We conducted a case-control study of medulloblastoma/primitive neuroectodermal tumors of brain (PNET) to pursue findings related to vitamin and mineral supplements, micronutrients, and cured meat consumption during gestation. Mothers of 315 cases ages <6 years at diagnosis in 1991 to 1997 identified from the United States and Canada through the Children's Oncology Group and mothers of 315 controls selected by random-digit dialing were interviewed. In the periconception period of the index pregnancy, case mothers were less likely than control mothers to report use of multivitamins [adjusted odds ratio (OR), 0.7; 95% confidence interval (95% CI), 0.4-1.0; $P = 0.08$] and to be in the highest quartile of iron and folate intake from food and supplements combined (adjusted OR for iron, 0.5; 95% CI, 0.3-0.9; $P_{trend} = 0.008$; adjusted OR for folate, 0.5; 95% CI, 0.3-0.9; $P_{trend} = 0.007$). Case and control mothers had similar intakes of cured meats, although case mothers were more likely to have the combination of high cured meat and low vitamin C intake (OR, 1.5; 95% CI, 1.0-2.3; $P = 0.08$). The results of the study add to the evidence of a protective role for multivitamins, suggest a possible role for micronutrients early in pregnancy, and generally do not support an association between cured meats and medulloblastoma/PNET. (Cancer Epidemiol Biomarkers Prev 2006;15(9):1660–7)

Introduction

Little is known about the etiology of childhood brain tumors, of which there are many histologic types. The second most common childhood brain tumor is the cerebellar medulloblastoma. Histologically similar tumors, called primitive neuroectodermal tumors of brain (PNET), occur in other parts of the central nervous system (1). Together, medulloblastoma and PNET account for ~20% of brain tumors in children (2), with ~80% of those being medulloblastoma (3). Medulloblastoma/PNET has a young age of onset, with half diagnosed before age 6 years (3), and is rare in adults. Most epidemiologic investigations of childhood brain tumors have included multiple histologic types, which would hinder the ability to identify risk factors, if etiology differs by tumor type.

In our previous study of medulloblastoma/PNET, several inverse associations were noted for maternal supplement use and intake of micronutrients during pregnancy. Use of multivitamins (early in pregnancy), use of iron, calcium, and vitamin C supplements, and high dietary folate and vitamin C intake from food were found to be associated with decreased risk (4). Although other data on medulloblastoma/PNET are limited, Preston-Martin et al. observed decreased odds ratios (OR) with increasing duration of multivitamin use during pregnancy (5).

Some of the previously reported findings on supplements and micronutrients are consistent with the hypothesis that exposure to N-nitroso compounds during the mother's pregnancy increases the risk of the child developing a brain tumor (6). N-nitroso compounds represent a class of substances that have been found to induce nervous system tumors in animals after low doses given transplacentally (7). Cured meats in the diet are a major source of N-nitroso compound precursors. The endogenous synthesis of N-nitroso compounds from precursors occurs in the stomach and elsewhere in the body (7) and reflects a major source of N-nitroso compound exposure. Some micronutrients, most notably vitamin C, inhibit the endogenous formation of N-nitroso compounds (8). Therefore, it has been hypothesized that women who eat large amounts of cured meats and have low vitamin C intake would be at increased risk for having a child with a brain tumor. As multivitamins contain sizeable quantities of vitamin C and other inhibitors of N-nitroso compound formation, the combination of high maternal cured meat intake in the absence of multivitamin use has been hypothesized to increase risk and elevated ORs consistent with the hypothesis have been observed for brain tumors in children (9).

To further investigate these findings, we conducted a case-control study of medulloblastoma/PNET focusing on maternal intake of supplements, micronutrients, and cured meats. As gestational exposures may be expected to act early in life, we studied children whose tumors were diagnosed at ages 0 to 5 years.

Materials and Methods

The study methods and the results for overall diet have been described in detail elsewhere (10). Briefly, eligible patients were diagnosed with medulloblastoma/PNET in the central nervous system before age 6 years, between 1991 and 1997, without a previous or concurrent cancer, and registered with the Children's Oncology Group through institutions previously affiliated with the legacy Children's Cancer Group.

Institutional review boards of all contributing institutions approved the study (Children's Cancer Group E-21). All participants provided informed consent.

Of the 558 potentially eligible cases, 120 were determined to be ineligible for the study because the physician did not give consent to contact family ($n = 35$), not medulloblastoma/PNET on pathology review ($n = 28$), biological mother not available ($n = 17$), language barrier ($n = 16$), no household phone ($n = 13$), residence outside North America ($n = 6$), prior or concurrent cancer ($n = 3$), and no response from institution ($n = 2$). In addition, institutions could not locate seven case families and parents of 39 cases did not respond to the institution's request or actively refused to allow their names and contact information to be released. On receiving permission from the treatment center to contact parents, 41 families could not be subsequently located and 27 families refused. We were unable to find controls for 6 cases. Thus, a total of 318 case-control sets were successfully interviewed and comprise the final sample.

We estimated misclassification of diagnosis by having one neuropathologist (L.B.R-A.) review slides or blocks when available. Cases with tumors judged not to be medulloblastoma/PNET were excluded. Based on the findings from 254 reviewed tumors, we estimated that 17 (5%) children in the final sample of 318 did not have medulloblastoma/PNET and are misclassified as cases (described in detail in ref. 10).

We used random-digit dialing to select control children who were matched to cases on area code, race (non-Hispanic white, non-Hispanic black, other), and date of birth (within 6 months for cases with age at diagnosis <1 year, within 1 year for older cases). The response rates (11) for the random-digit dialing screening call and the study questionnaire were 67% and 73%, respectively.

Trained interviewers conducted telephone interviews with mothers of cases and controls. The median interview length was 58 minutes (range, 25-135 minutes). Case interviews were a median of 1.6 years after the child's diagnosis (range, 0.1-6.2).

The interview included a food frequency questionnaire (FFQ) with 112 items. We modified the Willett FFQ (12) to investigate two periods during pregnancy and food groups of particular interest (cured meats, fruits, and vegetables) in greater detail. Data on portion size were not collected. For each item, the interviewer asked first about the subject's intake in the year before pregnancy and then about intake of the same item during the second trimester of pregnancy. We used diet in the year before pregnancy to estimate diet very early in pregnancy, before most women know they are pregnant; we refer to this period as periconception. Three individuals reported improbable energy intake (>6,000 or <500 kcal) or "don't know" responses to >20 foods in either period. The three affected pairs were excluded, leaving a final sample of 315 cases and 315 controls.

We collected data on supplement use in the year before the pregnancy and during the pregnancy. For multivitamins used in the year before the pregnancy, we asked about frequency of use, type, brand, and whether the mother was taking these supplements when the pregnancy began. For use during pregnancy, we asked about the month of pregnancy in which use started and ended, frequency of use, type, brand, and whether they were prescription or over-the-counter supplements. For eight individual supplements (vitamin A, β-carotene, vitamin C, vitamin E, folic acid, selenium, iron, and calcium), we asked about frequency of use, dose, use when the pregnancy began, and month of pregnancy in which use started and ended.

Women were considered to have used a supplement at conception if they reported use in the year before the pregnancy and that they were taking the supplement when they became pregnant. Women who did not report use in the year before the pregnancy were considered to have use at conception if they indicated they were taking the supplement before they became pregnant, in answer to a question about the month of pregnancy when use began. We defined patterns of

supplement use across periods. Whenever a woman began taking multivitamins, she generally continued taking them until the end of the pregnancy. About 95% of subjects had one of four patterns of multivitamin use: no use, use starting before or close to conception and continuing until the end of the pregnancy, use starting during the first trimester and continuing, or use starting during the second trimester and continuing. Patterns of use of commonly used individual supplements were similarly defined.

For cured meats, the total number of servings per day was calculated by summing the number of servings per day of the seven constitutive foods. Intake of individual cured meats and cured meats as a group was categorized based on the distribution in cases and controls combined. Intake of individual cured meats was categorized into two to four levels, determined by the distribution. For example, as few women reported frequent eating of smoked fish, two categories were defined. For commonly eaten foods, such as ham, four levels were defined. For cured meats as a group, the four levels approximated quartiles, with cut points that were integers or halves. The same cut points were used for periconception and midpregnancy.

Vitamin C, vitamin E, calcium, iron, and folate were examined because of their previous association with medulloblastoma/PNET and/or their ability to inhibit the formation of N-nitroso compounds from precursors. Other micronutrients were investigated in exploratory analyses. Intake of micronutrients was estimated from the number of servings per day and the micronutrient content of each food item in the FFQ, assuming a standard portion size, as we did not ask mothers to report portion size. Micronutrient intake from multivitamins was based on the brand and type of multivitamin reported. When brand and type were not reported or the brand/type combination was not in the database (12), we categorized the multivitamin as prescription or nonprescription and prenatal or not prenatal based on the mother's report and assigned her the micronutrient content of a typical prescription prenatal, nonprescription prenatal, or nonprenatal multivitamin accordingly. Nutrient intake from food alone and from food and supplements was calculated. Nutrient intake was energy adjusted by the residual method (13) and categorized into quartiles based on the distribution in cases and controls combined.

We investigated the effect of high cured meat intake with low vitamin C intake and of high cured meat intake in the absence of multivitamin use. For cured meats and multivitamins, we created two definitions of "exposure": (a) those in the highest quartile of cured meat consumption who did not take multivitamins and (b) those in the top half of cured meat consumption who did not take multivitamins. Similarly, for vitamin C and cured meats, we considered as exposed those in the highest quartile of cured meat consumption who were also in the lowest quartile of vitamin C intake from food and supplements and those in the top half of cured meat consumption who were also in the lower half of vitamin C intake.

The relationship between medulloblastoma/PNET and the dietary factors in each period was analyzed by unconditional logistic regression using indicator variables. The dietary factor of interest was examined by itself (crude analysis) and with covariates (adjusted analysis). Because the study design was matched, the matching factors (date of birth, race, and area code) were considered covariates. Although we present the results of unconditional logistic regression, we also did conditional logistic regression for all noteworthy findings. The results did not differ appreciably.

We matched controls to cases on area code to account for broad geographic differences in diet and other exposures. For the analysis, we divided the U.S. states and Canadian provinces into 14 geographic regions. Controls were consistently older

than cases and interviewed later because an individually matched control could not be sought until the case was interviewed. The inclusion of date of birth (matching factor), date of mother's interview, and age of child at interview in the same model created perfect multicolinearity (i.e., any two of the variables determined the third). We chose to include the date of interview and the child's age at interview in the models. Other possible covariates were income level, mother's educational level, maternal smoking, number of cigarettes per day, breast-feeding, duration of breast-feeding, residential mobility (number of moves), mother's body mass index, number of weeks of nausea, number of weeks of vomiting, and weight gain due to nausea or vomiting. The final models for use of supplements and combinations of cured meats, multivitamins, and vitamin C included mother's race, date of interview, child's age at interview, income level, number of cigarettes per day, and weight gain due to nausea or vomiting, because these altered one or more coefficients of the dietary factor by at least 15%, differed significantly or nearly so between cases and controls, or were matching factors. Models for micronutrients with and without supplements included total calories in addition to the possible confounders listed above. Geographic area did not change the results appreciably and was excluded.

We did tests for trend to evaluate evidence of dose-response relationships for micronutrient intake and cured meat intake.

The median intake for each level of a dietary factor was weighed by the mean of the medians so that the weights summed to 0. Individuals were assigned the weights for the relevant category as their value and logistic regression was done.

Most analyses were done using SPSS (14). SAS was used for conditional logistic regression (15).

Results

Case and control mothers were similar in age, prepregnancy weight, height, pregnancy weight gain, and nausea and vomiting during pregnancy (Table 1). Case mothers were less likely to have smoked in the month before or during pregnancy (21% versus 29%; $P = 0.02$). At the time of the mother's interview, controls were older than cases (mean ± SD, 4.9 ± 2.1 and 5.6 ± 2.3 years, respectively; $P < 0.001$ for case-control difference).

Supplements. We first examined the use of multivitamins in relation to medulloblastoma/PNET (Table 2). Use of multivitamins close to conception was associated with a decreased risk of borderline significance [adjusted OR, 0.7; 95% confidence interval (95% CI), 0.4-1.0; $P = 0.08$]. The same effect can be seen in the results by pattern of use; compared with the reference group of women who began using multivitamins before or close

Table 1. Demographic and pregnancy characteristics of participants in a case-control study of medulloblastoma/PNET in children ages 0 to 6 years

Characteristics	Case, n (%)	Control, n (%)	P*
Mother's race	315 (100)	315 (100)	0.91
White, non-Hispanic	257 (82)	264 (84)	
Black, non-Hispanic	16 (5)	14 (4)	
Hispanic	31 (10)	27 (9)	
Other	11 (3)	10 (3)	
Mother's education	315 (100)	315 (100)	0.70
Less than high school	28 (9)	37 (12)	
High school	87 (28)	83 (26)	
Some post-high school	99 (31)	105 (33)	
College graduate	76 (24)	67 (21)	
Professional or graduate school	25 (8)	23 (7)	
Mother's marital status at interview	315 (100)	315 (100)	0.35 [†]
Married	264 (84)	255 (81)	
Separated, divorced, widowed	28 (9)	32 (10)	
Single	23 (7)	28 (9)	
Household income	297 (100)	285 (100)	0.06 [‡]
<$15,000	42 (14)	48 (17)	
$15,000-24,999	49 (16)	56 (20)	
$25,000-34,999	53 (18)	53 (19)	
$35,000-49,999	67 (23)	63 (22)	
$50,000-75,000	52 (18)	41 (14)	
>$75,000	34 (11)	24 (8)	
Age of child at interview [mean (SD)]	315 [4.9 (2.1)]	315 [5.6 (2.3)]	<0.001
Date interviewed in months since start of study [mean (SD)]	315 [15.8 (10.6)]	315 [23.5 (8.9)]	<0.001
Mother's age at birth of index child [mean (SD)]	315 [28.2 (5.4)]	314 [28.3 (5.8)]	0.97
Nausea during index pregnancy	315 (100)	314 (100)	0.41
Yes	193 (61)	203 (65)	
No	122 (39)	111 (35)	
Vomiting during index pregnancy	315 (100)	314 (100)	0.62
Yes	116 (37)	109 (35)	
No	199 (63)	205 (65)	
Prepregnancy weight [mean (SD)]	311 [135.9 (23.6)]	309 [136.4 (29.4)]	0.79
Pregnancy weight gain [mean (SD)]	309 [33.9 (14.2)]	311 [33.0 (14.2)]	0.40
Gained weight due to pregnancy nausea or vomiting	311 (100)	313 (100)	0.006
Yes	26 (8)	10 (3)	
No	282 (92)	301 (97)	
Smoked during index pregnancy	315 (100)	315 (100)	0.03
Yes	65 (21)	90 (29)	
No	250 (79)	225 (71)	
No. cigarettes per day during index pregnancy (smokers only) [mean (SD)]	34 [8.3 (5.5)]	58 [10.9 (8.3)]	0.01

*P for case-control comparison by Fisher's exact or t test unless otherwise noted.
[†]P for married versus single, separated, divorced, or widowed.
[‡]P based on logistic regression of income as a continuous variable using the midpoint of each category as the value.

Table 2. Results for supplement use during pregnancy by period and pattern from a case-control study of medulloblastoma/PNET in children ages 0 to 6 years

Supplement	n	Crude OR (95% CI)	P	Adjusted* OR (95% CI)	P
Multivitamin					
Any	581	1.3 (0.7-2.4)	0.36	1.2 (0.6-2.4)	0.66
Period					
Conception	147	0.8 (0.6-1.2)	0.34	0.7 (0.4-1.0)	0.08
Trimester 1	537	1.0 (0.7-1.6)	0.91	0.9 (0.5-1.6)	0.80
Trimester 2	563	1.3 (0.8-2.2)	0.34	1.2 (0.6-2.2)	0.61
Trimester 3	551	1.2 (0.7-1.9)	0.61	1.0 (0.6-1.9)	0.90
Pattern of use [†]					
No use	46	0.9 (0.5-1.8)	0.77	1.2 (0.5-2.7)	0.67
Use starting close to conception [‡] (reference)	137	1.0		1.0	
Use starting in trimester 1	359	1.2 (0.8-1.9)	0.27	1.6 (1.0-2.5)	0.05
Use starting in trimester 2	37	1.4 (0.7-2.9)	0.38	1.5 (0.7-3.6)	0.32
Duration (increase of 1 mo)	617	1.00 (0.9-1.1)	0.99	0.99 (0.9-1.1)	0.71
Calcium					
Any	96	0.9 (0.6-1.3)	0.58	0.8 (0.5-1.2)	0.27
Period					
Conception	52	0.8 (0.5-1.5)	0.56	0.6 (0.3-1.2)	0.15
Trimester 1	78	0.8 (0.5-1.4)	0.54	0.8 (0.4-1.3)	0.35
Trimester 2	110	0.8 (0.5-1.2)	0.34	0.7 (0.4-1.1)	0.10
Trimester 3	115	0.7 (0.5-1.1)	0.15	0.6 (0.4-1.0)	0.06
Pattern of use [†]					
No use (reference)	472	1.0		1.0	
Use close to conception only	16	1.0 (0.4-2.6)	0.96	0.6 (0.2-2.0)	0.45
Use starting close to conception	29	0.5 (0.2-1.1)	0.10	0.4 (0.2-1.0)	0.06
Use starting in trimester 1	37	0.8 (0.4-1.6)	0.58	0.9 (0.4-1.9)	0.76
Use starting in trimester 2	36	0.9 (0.4-1.7)	0.69	0.6 (0.3-1.2)	0.14
Folic acid					
Any	18	0.8 (0.3-2.0)	0.81	1.1 (0.4-3.2)	0.86
Iron					
Any	107	0.7 (0.5-1.1)	0.17	0.9 (0.5-1.4)	0.60
Period					
Conception	40	0.9 (0.5-1.7)	0.87	0.8 (0.4-1.6)	0.46
Trimester 1	89	0.8 (0.5-1.2)	0.30	1.0 (0.6-1.8)	0.96
Trimester 2	144	0.8 (0.5-1.1)	0.18	0.8 (0.5-1.2)	0.28
Trimester 3	141	0.8 (0.6-1.2)	0.39	0.8 (0.5-1.3)	0.35
Pattern of use [†]					
No use (reference)	446	1.0		1.0	
Use starting close to conception	20	0.9 (0.4-2.2)	0.84	0.6 (0.2-1.8)	0.36
Use starting in trimester 1	57	0.8 (0.4-1.3)	0.35	1.0 (0.5-2.1)	0.90
Use starting in trimester 2	56	0.8 (0.5-1.4)	0.41	0.7 (0.4-1.3)	0.25
Vitamin C					
Any	58	1.4 (0.8-2.4)	0.27	1.4 (0.7-2.6)	0.30
Vitamin E					
Any	15	1.2 (0.4-3.2)	0.80	1.0 (0.3-3.2)	0.97

*Adjusted for mother's race, date of interview, child's age at interview, income, number of cigarettes smoked per day, total calories, and maternal weight gain (yes/no) because of pregnancy nausea/vomiting; the n is 572 because of missing data for income level and gained weight.

[†]Use continued from the specified start of use until the end of the pregnancy unless otherwise noted.

[‡]The reference group for multivitamin use is the group who began use close to conception instead of those who did not use the supplement at any time during the pregnancy. For multivitamins, the small number of never users would have resulted in imprecise estimates of the OR; we chose a larger group as the reference group.

to conception, the adjusted ORs for other patterns are elevated. Duration of multivitamin use during pregnancy showed no association with medulloblastoma/PNET.

We next examined the use of individual vitamin and mineral supplements (Table 2). For calcium supplements, we observed decreased risk that approached significance for use during the third trimester (OR, 0.6; 95% CI, 0.4-1.0; P = 0.06) and use starting close to conception and continuing throughout the pregnancy (OR, 0.4; 95% CI, 0.2-1.0; P = 0.06). We observed no strong associations with use of iron supplements. The ORs by period and pattern were between 0.6 and 1.0, but none were statistically significant. Few women reported taking vitamin C, vitamin E, or folic acid supplements; analysis was limited to use at any time during the pregnancy compared with no use (Table 2) and no associations were observed. The small number of women who took vitamin A, β-carotene, or selenium precluded analysis.

Micronutrients. The results for selected micronutrients from food alone and from food and supplements combined are presented in Table 3. For calcium with or without supplements, we observed little evidence of influence on risk.

Folate from food alone showed no strong associations. When supplements were included, the adjusted OR (95% CI) for the highest quartile in the periconception period was 0.5 (0.3-0.9) and the trend was statistically significant (P_{trend} = 0.007).

ORs for the highest quartile of iron without supplements were modestly and nonsignificantly decreased, with no strong indication of a dose-response relationship. When intake from supplements was included, the results in the periconception period became stronger with a significant adjusted OR (95% CI) of 0.5 (0.3-0.9) in the highest quartile (P_{trend} = 0.008).

For vitamin C from food alone, a decreased risk was generally observed for all quartiles above the reference category, with the third quartile adjusted ORs reaching significance (OR, 0.5; 95% CI, 0.3-0.9; P < 0.05) in midpregnancy. When intake from supplements was added, the adjusted OR for the third quartile in midpregnancy remained the same and statistically significant, but no trend across quartiles was observed.

There was a slight indication of an increasing trend for periconception intake of vitamin E from food alone and a decreasing trend for midpregnancy intake from food and supplements.

For the periconception period, the results for calcium, folate, iron, vitamin C, and vitamin E from food alone were not appreciably different when the analysis was limited to mothers who did not use supplements. The analogous analyses could not done for midpregnancy, as the vast majority of mothers used supplements at that time.

Results for other micronutrients from food alone have been reported elsewhere (10). No statistically significant or otherwise noteworthy trends were observed for intake of the B vitamins, vitamin A, vitamin D, sodium, or zinc from food and supplements combined (data not shown).

Cured Meats. There was no indication of increased risk for frequent consumption of individual cured meats, cured meats as a group, or cured meats as a group in the absence of multivitamin use (Tables 4 and 5). The ORs for the combination of having cured meat intake in the top half and vitamin C in the bottom half were slightly elevated, ranging from 1.1 to 1.5, but were not statistically significant.

Discussion

We presented the results concerning the role of several components of diet—vitamin and mineral supplements, micronutrients, and cured meats, all of which have been reported previously to affect the risk of childhood brain tumors. These dietary factors are further related in that vitamin supplements contain micronutrients, several of which are hypothesized to modify the effect of *N*-nitroso compounds on risk of childhood brain tumors, and cured meats are a major source of *N*-nitroso compound precursors. The study reported here collected more

Table 3. Results by period for selected energy-adjusted nutrients with and without supplements from a case-control study of medulloblastoma/PNET in children ages 0 to 6 years

Nutrient	Periconception			Midpregnancy		
	Quartile ranges	Crude OR (95% CI)	Adjusted* OR (95% CI)	Quartile ranges	Crude OR (95% CI)	Adjusted* OR (95% CI)
Calcium without supplements (mg)	<537	1.0	1.0	<579	1.0	1.0
	537-627	1.0 (0.7-1.6)	1.1 (0.6-1.8)	579-679	0.8 (0.5-1.3)	0.9 (0.6-1.6)
	628-726	1.3 (0.8-2.0)	1.2 (0.7-2.0)	680-792	1.3 (0.8-2.0)	1.1 (0.6-1.8)
	≥727	1.1 (0.7-1.7)	1.1 (0.6-1.8)	≥793	1.1 (0.7-1.8)	1.1 (0.6-1.9)
	P_{trend}	0.51	0.85	P_{trend}	0.30	0.64
Calcium with supplements (mg)	<547	1.0	1.0	<804	1.0	1.0
	547-649	0.9 (0.6-1.4)	0.9 (0.6-1.6)	804-919	1.1 (0.7-1.7)	1.1 (0.7-1.9)
	650-769	1.4 (0.9-2.2)	1.1 (0.6-1.8)	920-1,062	1.1 (0.7-1.7)	0.9 (0.6-1.6)
	≥770	1.0 (0.6-1.6)	0.9 (0.5-1.6)	≥1,063	1.2 (0.8-1.9)	0.9 (0.6-1.6)
	P_{trend}	0.71	0.80	P_{trend}	0.42	0.71
Folate without supplements (μg)	<267	1.0	1.0	<279	1.0	1.0
	267-322	1.3 (0.8-2.0)	1.1 (0.7-1.9)	279-332	1.2 (0.8-1.9)	1.3 (0.7-2.1)
	323-379	1.0 (0.7-1.6)	1.0 (0.6-1.7)	333-403	1.0 (0.7-1.6)	1.0 (0.6-1.8)
	≥380	1.3 (0.8-2.1)	1.2 (0.7-2.0)	≥404	1.1 (0.7-1.6)	1.0 (0.6-1.6)
	P_{trend}	0.33	0.65	P_{trend}	0.84	0.67
Folate with supplements (μg)	<286	1.0	1.0	<961	1.0	1.0
	286-347	0.9 (0.6-1.5)	0.9 (0.5-1.5)	961-1,276	0.9 (0.6-1.4)	0.7 (0.4-1.1)
	348-482	1.1 (0.7-1.8)	1.3 (0.8-2.2)	1,277-1,364	1.0 (0.6-1.5)	0.9 (0.5-1.5)
	≥483	0.7 (0.5-1.1)	0.5 [†] (0.3-0.9)	≥1,365	1.0 (0.7-1.6)	0.8 (0.5-1.3)
	P_{trend}	0.09	0.007	P_{trend}	0.95	0.33
Iron without supplements (mg)	<12	1.0	1.0	<12.0	1.0	1.0
	12-13.6	0.9 (0.6-1.4)	0.8 (0.5-1.4)	12.1-14.1	0.9 (0.6-1.4)	0.8 (0.5-1.4)
	13.7-16.3	1.1 (0.7-1.7)	1.2 (0.7-2.1)	14.2-16.9	0.8 (0.5-1.3)	1.0 (0.6-1.6)
	≥16.4	0.8 (0.5-1.3)	0.8 (0.5-1.3)	≥17.0	0.8 (0.5-1.2)	0.7 (0.4-1.2)
	P_{trend}	0.44	0.44	P_{trend}	0.26	0.21
Iron with supplements (mg)	<12.4	1.0	1.0	<68	1.0	1.0
	12.4-14.8	0.8 (0.5-1.3)	0.8 (0.5-1.4)	68-75	0.9 (0.6-1.4)	0.8 (0.5-1.4)
	14.9-21.2	0.9 (0.6-1.4)	0.8 (0.5-1.4)	76-89	1.0 (0.7-1.6)	1.0 (0.6-1.6)
	≥21.3	0.7 (0.4-1.0)	0.5 [†] (0.3-0.9)	≥90	0.7 (0.5-1.1)	0.7 (0.4-1.1)
	P_{trend}	0.10	0.008	P_{trend}	0.15	0.11
Vitamin C without supplements (mg)	<125	1.0	1.0	<135	1.0	1.0
	125-169	0.9 (0.6-1.4)	0.8 (0.4-1.3)	136-184	0.7 (0.4-1.0)	0.6 (0.3-1.0)
	170-223	0.9 (0.5-1.4)	0.8 (0.5-1.4)	185-240	0.6 [†] (0.4-1.0)	0.5 [†] (0.3-0.9)
	≥224	0.9 (0.6-1.4)	0.7 (0.4-1.2)	≥241	0.7 (0.5-1.1)	0.6 (0.4-1.1)
	P_{trend}	0.73	0.31	P_{trend}	0.22	0.13
Vitamin C with supplements (mg)	<133	1.0	1.0	<215	1.0	1.0
	134-190	0.8 (0.5-1.3)	0.9 (0.5-1.5)	216-266	0.8 (0.5-1.2)	0.6 (0.3-1.0)
	191-261	0.9 (0.6-1.4)	0.9 (0.5-1.5)	267-329	0.7 (0.5-1.1)	0.5 [†] (0.3-0.9)
	≥262	0.9 (0.6-1.4)	0.9 (0.5-1.5)	≥330	1.0 (0.6-1.6)	0.9 (0.5-1.5)
	P_{trend}	0.92	0.75	P_{trend}	0.93	0.71
Vitamin E without supplements (IU)	<7.0	1.0	1.0	<7.3	1.0	1.0
	7.0-8.1	1.1 (0.7-1.6)	1.1 (0.6-1.8)	7.3-8.5	0.9 (0.6-1.4)	0.7 (0.4-1.2)
	8.2-9.5	1.0 (0.7-1.6)	1.2 (0.7-2.0)	8.6-10.1	0.8 (0.5-1.3)	0.9 (0.5-1.5)
	≥9.6	1.2 (0.8-1.9)	1.4 (0.8-2.3)	>10.1	1.0 (0.6-1.5)	1.0 (0.6-1.6)
	P_{trend}	0.46	0.21	P_{trend}	0.98	0.77
Vitamin E with supplements (IU)	<7.2	1.0	1.0	≤20	1.0	1.0
	7.3-9.8	1.0 (0.6-1.5)	1.2 (0.6-2.1)	21-35	1.0 (0.6-1.5)	1.1 (0.7-1.9)
	9.9-13.6	1.1 (0.7-1.7)	1.6 (0.8-3.1)	36-39	0.7 (0.5-1.1)	0.7 (0.4-1.3)
	≥13.7	0.9 (0.6-1.5)	0.9 (0.5-1.6)	≥40	0.8 (0.5-1.3)	0.8 (0.5-1.4)
	P_{trend}	0.72	0.24	P_{trend}	0.18	0.27

*Adjusted for mother's race, date of interview, child's age at interview, income, number of cigarettes smoked per day, total calories, and maternal weight gain (yes/no) because of pregnancy nausea/vomiting.
[†] $P < 0.05$ for quartile OR.

Table 4. Results for maternal intake of individual cured meats and cured meats as a group from a case-control study of medulloblastoma/PNET in children ages 0 to 6 years

Food group and no. servings	Periconception			Midpregnancy		
	n	Crude OR (95% CI)	Adjusted* OR (95% CI)	n	Crude OR (95% CI)	Adjusted* OR (95% CI)
Ham						
<1/mo	150	1.0	1.0	168	1.0	1.0
1-3/mo	244	1.1 (0.8-1.7)	1.4 (0.9-2.3)	231	1.2 (0.8-1.8)	1.5 (0.9-2.4)
1/wk	151	1.2 (0.8-1.9)	1.4 (0.8-2.5)	144	1.1 (0.7-1.8)	1.3 (0.8-2.2)
>1/wk	84	0.9 (0.5-1.6)	0.9 (0.5-1.8)	86	1.0 (0.6-1.8)	0.9 (0.5-1.8)
P_{trend}		0.70	0.58		1.00	0.54
Lunchmeat						
<1/mo	323	1.0	1.0	333	1.0	1.0
1-3/mo	130	1.2 (0.8-1.9)	1.5 (0.9-2.4)	126	1.2 (0.8-1.6)	1.5 (0.9-2.5)
1/wk	102	0.9 (0.6-1.5)	0.9 (0.5-1.5)	96	1.1 (0.7-1.8)	1.0 (0.6-1.8)
>1/wk	74	0.8 (0.5-1.3)	1.0 (0.5-1.8)	74	0.8 (0.5-1.4)	0.9 (0.5-1.6)
P_{trend}		0.38	0.86		0.52	0.75
Hot dogs						
<1/mo	245	1.0	1.0	260	1.0	1.0
1-3/mo	242	1.2 (0.8-1.7)	1.2 (0.8-1.9)	230	1.1 (0.8-1.6)	1.2 (0.8-1.8)
≥1/wk	143	0.9 (0.6-1.3)	0.8 (0.5-1.4)	140	0.9 (0.6-1.4)	0.9 (0.6-1.5)
P_{trend}		0.69	0.83		0.89	0.95
Lunch sausage						
<1/mo	431	1.0	1.0	442	1.0	1.0
≥1/mo	199	1.1 (0.8-1.6)	1.1 (0.7-1.6)	188	1.0 (0.7-1.4)	1.1 (0.7-1.6)
P_{trend}		0.55	0.65		0.86	0.81
Pizza with pepperoni, salami, or sausage						
<1/mo	175	1.0	1.0	206	1.0	1.0
1-3/mo	270	0.9 (0.6-1.3)	0.9 (0.6-1.4)	250	1.0 (0.7-1.4)	1.1 (0.7-1.7)
≥1/wk	185	1.0 (0.7-1.5)	1.1 (0.6-1.7)	174	1.1 (0.7-1.7)	1.2 (0.7-1.9)
P_{trend}		0.96	0.90		0.64	0.53
Smoked fish or lox						
<1/mo	584	1.0	1.0	584	1.0	1.0
≥1/mo	47	1.1 (0.6-2.1)	1.3 (0.7-2.6)	46	1.1 (0.6-2.0)	1.3 (0.6-2.6)
P_{trend}		0.65	0.42		0.76	0.47
Cured meat and fish						
<2/wk	162	1.0	1.0	181	1.0	1.0
2 to <3.5/wk	182	1.1 (0.7-1.7)	1.4 (0.8-2.2)	176	0.9 (0.6-1.3)	1.1 (0.7-1.9)
≥3.5 to ≤5/wk	134	1.0 (0.6-1.6)	1.1 (0.6-1.9)	119	1.0 (0.6-1.6)	1.1 (0.6-2.0)
>5/wk	152	0.9 (0.6-1.5)	1.0 (0.6-1.9)	154	1.0 (0.6-1.5)	1.0 (0.6-1.8)
P_{trend}		0.63	0.81		0.89	0.99

*Adjusted for income level, mother's race, age of child at interview, date of interview, gained weight as a result of nausea/vomiting, number cigarettes per day, and total calories.

detailed dietary and supplement data compared with previous studies of childhood brain tumors.

We observed an inverse association with multivitamin use close to conception. In our previous study of medulloblastoma/PNET, the OR for multivitamin use in a similar period was 0.6 and was statistically significant (4). The observation in the current study is weaker, as the OR is 0.7 and of only borderline significance, but as it is similar to our previous finding, we believe that it is unlikely to have occurred by chance. In contrast to our findings, Preston-Martin et al. did not observe an association between multivitamin use in the periconception period (5), although results are not presented for medulloblastoma/PNET separately. However, they did observe an effect of duration of use for medulloblastoma/PNET; multivitamin use during at least two trimesters seemed to decrease risk. In the current study, we observed no association with duration.

Table 5. Results for maternal intake of cured meat with low vitamin C intake or absence of multivitamin use from a case-control study of medulloblastoma/PNET in children ages 0 to 6 years

Cured meat, vitamin C, and multivitamin combination	Periconception					Midpregnancy				
	n	Crude OR (95% CI)	P	Adjusted* OR (95% CI)	P	n	Crude OR (95% CI)	P	Adjusted* OR (95% CI)	P
Top half of cured meats/no multivitamins										
No		1.0		1.0			1.0		1.0	
Yes	221	1.1 (0.8-1.5)	0.56	1.1 (0.8-1.7)	0.50	29	0.7 (0.3-1.5)	0.34	0.8 (0.3-2.0)	0.64
Top quartile of cured meats/no multivitamins										
No		1.0		1.0			1.0		1.0	
Yes	123	0.9 (0.6-1.3)	0.61	0.9 (0.6-1.5)	0.82	18	0.5 (0.2-1.3)	0.16	0.6 (0.2-1.9)	0.34
Top half of cured meats/bottom half of vitamin C										
No		1.0		1.0			1.0		1.0	
Yes	151	1.1 (0.8-1.6)	0.51	1.2 (0.8-1.9)	0.39	153	1.3 (0.9-1.8)	0.23	1.5 (1.0-2.3)	0.08
Top quartile of cured meats/bottom quartile of vitamin C										
No		1.0		1.0			1.0		1.0	
Yes	55	1.0 (0.6-1.7)	0.89	1.1 (0.6-2.1)	0.85	64	0.9 (0.5-1.5)	0.60	1.1 (0.6-2.1)	0.75

*Adjusted for mother's race, date of interview, child's age at interview, income, number of cigarettes smoked per day, and maternal weight gain (yes/no) because of pregnancy nausea/vomiting.

Together, the evidence suggests a protective role for multivitamins, although whether duration or timing of use in relation to conception is the critical aspect is not clear. It is also not clear what component of multivitamins might be critical; folate, vitamin A, vitamin C, vitamin D, and vitamin E have been suggested (5).

The findings for most of the micronutrients are difficult to interpret as the results vary by whether the source is an individual supplement, foods, or foods plus individual supplements and multivitamins. For example, modest but not statistically significant inverse associations with iron supplements were observed, but increasing iron intake from foods did not show a convincing trend. However, for iron intake from food and all supplements, a statistically significant trend was observed in the periconception period. As the highest quartile largely determined the trend, a possible explanation is an effect of iron that occurs only at high levels of intake, which are achieved mostly by supplements (iron supplements and/or multivitamins). In the previous study, the data collected did not permit the calculation of iron intake, but we did observe an inverse association with iron supplements (4). The results of the two studies can be seen as consistent in that both suggest a possible protective role of iron.

Although not statistically significant, nearly all the results for calcium supplements showed decreased risk, with use close to conception or during the third trimester having the strongest effects, some of borderline significance. However, high calcium intake from food alone or from food and supplements combined showed no indication of decreased risk. Possible reasons for the discrepant findings include chance and an effect specific to calcium supplements. Previously, we observed a significant inverse association of medulloblastoma/PNET with use of calcium supplements at any time during the pregnancy (4). The results reported here for calcium supplements are somewhat consistent with the previous study, but weaker.

High folate intake from food was associated with decreased risk in our previous study of medulloblastoma/PNET (4). In the results presented here, no evidence of a trend was observed for folate from food. The FFQ of the previous study did not include all foods rich in folate and thus represents a less rigorous assessment compared with the current study. When intake from supplements was included, the results differed from those for food alone; periconception intake in the highest quartile was significantly associated with a 50% reduction in risk. The results were unchanged when the seven women who reported taking folate supplements (not as part of a multivitamin) close to conception were excluded. Folate fortification of grains did not affect our estimates of intake because all the pregnancies studied occurred before fortification began. Similar to the results for iron, the results for folate are consistent with a protective effect of high doses close to conception.

The other two micronutrients studied, vitamins C and E, were chosen because of their relation to the hypothesis that gestational exposure to N-nitroso compounds increases the risk of childhood brain tumors and because they are antioxidants. Vitamin C and, to a lesser extent, vitamin E inhibit the endogenous formation of N-nitroso compounds from precursors that occur in foods (8). In animals, vitamin C can completely eliminate tumor induction from N-nitroso compound precursors (16). Thus, under the N-nitroso compound hypothesis, low vitamin C intake, low vitamin E intake, and the combination of low vitamin C intake and high cured meat intake are predicted to increase risk.

In the data presented here, there was no suggestion of an increased risk associated with frequent eating during pregnancy of cured meats either individually or as a group. Although frequent consumption of cured meats during pregnancy has been associated with childhood brain tumors in many studies (6, 9, 17-20), medulloblastoma/PNET comprised a minority of the cases in those studies or were excluded completely. Our previous study of medulloblastoma/PNET also found no association with cured meats as a group but a significant association with bacon (4).

Some indication for an inverse association with vitamin C was seen when intake from food alone was considered. The three highest quartiles showed decreased risks of similar magnitude especially in midpregnancy, but including intake from supplements substantially weakened the apparent threshold effect. Possible explanations of these vitamin C results include an effect of a substance that occurs in many of the same foods as vitamin C but not in supplements and/or inaccurate reporting of vitamin C supplement use. There is some evidence for the latter as 40% of those who took vitamin C during the pregnancy did not take it daily, which may indicate irregular use. Medications that are not used regularly may be reported less accurately than others (21). No association with vitamin E was observed.

For the combination of low intake of vitamin C and high intake of cured meats, we observed modestly increased risks for this combination in midpregnancy. Not taking multivitamins (which contain vitamins C and E) during pregnancy in conjunction with frequent cured meat consumption did not increase risk, in contrast to previous reports for all brain tumor types combined (9, 17). However, our FFQ like most others is not detailed enough to investigate this aspect of the N-nitroso compound hypothesis. If the N-nitroso compound precursors and the inhibitors need to be present in the stomach at the same time, as has been suggested (9), the FFQ would need to include additional questions about what foods are eaten together and with what foods supplements are usually taken.

In total, the data presented here provide, at best, modest support for the N-nitroso compound hypothesis in relation to medulloblastoma/PNET. Both in this study and in our previous study of this histologic group (4), cured meats as a group and individually were not associated with risk. As we have discussed elsewhere in more detail, the weight of the evidence suggests that cured meats are not associated with medulloblastoma/PNET (10). However, we did observe some indication of decreased risk associated with vitamin C and increased risk associated with the combination of high cured meat intake and low vitamin C intake, findings consistent with the N-nitroso compound hypothesis.

The results presented here are based on self-report and thus are subject to misclassification of exposure. Studies of reproducibility and validity of FFQ have shown that adults can report their diet, including during pregnancy, up to 10 years in the past reasonably well (22, 23). However, recent findings suggest that FFQ may be less valid and less able to detect nutrient-cancer associations than thought previously (24). In contrast to diet, the accuracy of self-reported supplement use is not well studied. The existing studies suggest that multivitamin use is well reported in the past year and in the previous 10 years (25-27). In two studies, use of single supplements of vitamins C and E was accurately reported, but use of calcium and iron supplements was less well reported (26, 27). To our knowledge, there are no published studies on the validity of reporting of supplements during a past pregnancy. If use during pregnancy is remembered as well as use during adult life generally, we would speculate that our results for multivitamins are more valid than those for iron and calcium.

The available data on recall bias in reporting of diet suggest that although it may occur, it may not occur consistently and may differ, for example, by cancer site (22). Whether mothers of children with a serious medical condition, such as the case mothers in this study and mothers of healthy control children, differ in their reporting of diet or supplement use has not been studied. In addition, selection bias may have occurred even

with reasonably high case and control response rates. Selection bias based on demographic factors seems unlikely to explain the results, as we adjusted for those that differed between cases and controls.

Chance may explain some of our findings, as we did ~75 comparisons. In addition to the likelihood of false-positive findings as a result of multiple comparisons, we may have failed to detect associations as well. The typical measurement error for dietary factors results in substantially lower power for a given sample size than if an exposure were measured without error (28).

In summary, we observed inverse associations with multivitamins, iron, and folate and weaker associations with calcium supplements and vitamin C. All of these findings are somewhat consistent with those from the previous study of medulloblastoma/PNET. However, the generally weaker results in this study, the lack of internal consistency between the findings for supplement use, intake from foods, and intake from foods and supplements combined, and recent findings on the deficiencies of FFQ (24) decrease our confidence in their validity. Interestingly, the findings for multivitamins, total iron, and total folate intake point to the time close to conception as a possible critical period. The study of this period presents methodologic challenges, as most women do not yet know they are pregnant. The retrospective assessment of multivitamin and other supplement use required in case-control studies adds challenges. Women must be asked to recall details of their use of supplements, at a time when they are unlikely to still be taking the same supplements because they are not pregnant at the time of interview and thus no longer have the supplement container with its dose information. The multitude of supplements on the market and the changes in their composition over time further add to the difficulty. Perhaps, questionnaires can be improved by designing questions that better focus on the periconception period and using photos as well as names of the most common prenatal multivitamin preparations as is done in pharmacoepidemiology (29).

Acknowledgments

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