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Prenatal vitamin supplementation and pediatric brain tumors: huge international variation in use and possible reduction in risk

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Abstract An international case-control study of primary pediatric brain tumors included interviews with mothers of cases diagnosed from 1976–1994 and mothers of population controls. Data are available on maternal vitamin use during pregnancy for 1051 cases and for 1919 controls in eight geographic areas of North America, Europe and Israel. While risk estimates varied by study center, combined results suggest that maternal supplementation for two trimesters may decrease risk of brain tumor [odds ratio (OR)=0.7; 95% confidence interval (CI)=0.5–0.9], with a trend toward less risk with longer duration of use (P trend=0.0007). The greatest risk reduction was among children diagnosed under

5 years of age whose mothers used supplements during all three trimesters (OR=0.5; CI=0.3–0.8). This effect did not vary by histology and was seen for supplementation during pregnancy rather than during the month before pregnancy or while breast feeding. These findings are largely driven by data from the US, where most mothers took vitamins. The proportion of control mothers who took vitamins during pregnancy varied tremendously, from 3% in Israel and in France through 21% in Italy, 33% in Canada, 52% in Spain to 86–92% at the three US centers. The composition of the various multivitamin compounds taken also varied: daily dose of vitamin C ranged from 0 up to 600 mg; vitamin E from 0 to 70 mg; vitamin A from 0 to 30,000 IU and folate from 0 to 2000 mg. Mothers also took individual micronutrient supplements (e.g., vitamin C tablets), but most mothers who took these also took multivitamins, making it impossible to determine potential independent effects of these micronutrients.

Key words Brain neoplasms · Childhood neoplasms · Prenatal exposures · Vitamin supplements

Introduction

Brain tumors are a leading cause of cancer deaths in children in developed countries [19]. Little is known about the causes of these tumors [5]. A family history of multiple nervous system tumors, which usually occur in association with predisposing genetic syndromes, appears to be a factor in fewer than 5% of cases [1]. Exposure to X-rays and to other forms of ionizing radiation is the only clearly established environmental cause but accounts for only a few percent of cases [24]. Many other suggested risk factors have been investigated, including head trauma, parental occupational exposures, use of medication, and diet [24]. This report looks at maternal use of prenatal vitamin supplements.

An incidental finding in an early case-control study of pediatric brain tumors provided the first indication that prenatal vitamin supplementation might be related to reduced brain tumor risk [25]. In this study, mothers were asked about use during pregnancy of several specific medications; in answer to a final question about "any other drugs," more control mothers than case mothers volunteered that they had taken prenatal vitamins [odds ratio (OR)=0.6] [25]. More than a decade later, several studies reported similarly decreased risk related to maternal use of prenatal vitamins; these include studies of specific histological subgroups of cases such as primitive neuroectodermal tumors (PNET) [4] and astrocytoma [5] and studies of all types of pediatric brain tumor combined [29]. In the largest study to date, decreased risk related to prenatal vitamin supplementation was apparent both for all types of tumors combined and for each of the three major subtypes (astroglial tumors, PNET, and other glial tumors) [26]. The present report includes data from this study, which was the US portion of an international collaborative study of childhood brain tumors, and also data from centers in France, Italy, Spain, Israel and Canada.

Methods

We investigated whether intake of vitamin supplements by mothers during pregnancy, during the month before pregnancy, or while breast feeding was related to risk of pediatric brain tumors, including each of three major histological subgroups of these tumors. Dose-response relationships were evaluated. The prevalence of vitamin intake across the countries in the study and the micronutrient content of supplements used were compared.

Subjects in this study were participants in the international population-based case-control study conducted to investigate risk factors for primary brain tumors in children. Investigators from nine centers (Paris, France; Milan, Italy; Valencia, Spain; Israel; Winnipeg, Canada; Los Angeles, San Francisco and Seattle, US; and Sydney, Australia) worked together to develop the international protocol, design a standard questionnaire and make decisions regarding study conduct and analysis. This study was coordinated by the International Agency for Research on Cancer (IARC) in Lyon, France, where data from the centers were compiled and merged into a com-

bined data set that includes 1218 cases and 2223 controls. Of these, maternal vitamin supplementation data were available for 1051 (86%) cases and 1919 (86%) controls. Analyses excluded subjects for whom vitamin supplementation data were not collected (all Sydney subjects and 35 cases (78%) and 58 controls (70%) from Winnipeg) and for whom information on vitamin supplementation was unknown (12 cases and 10 controls from Milan, Paris, and Valencia.)

Controls were frequency matched to cases in all US centers and in Paris; otherwise they were individually matched. Matching variables were sex, age, and, at five centers (Seattle, Winnipeg, Valencia, Milan, and Israel), geographic region. Cases were diagnosed during a range of years from 1976–1994; in Israel, cases were diagnosed during 1976–1992; in Paris, 1985–1987; in Milan, 1984–1988; in Valencia, 1983–1990; in Los Angeles, 1984–1991; and in Seattle and San Francisco, 1984–1990. Diagnosis years in Winnipeg were 1980–1994, but questions concerning maternal vitamin use were added to the questionnaire used there only in the final years of the study. The range of age at diagnosis covered birth to 19 years overall, with some variation in the upper age by study center. The maximum age included was 19 years in all US centers and in Israel and Winnipeg; 16 years in Milan; 15 years in Paris; and 14 years in Valencia. A "reference age" and a "reference date" were defined for each control. In the US, these were the age and the date when the control reached the age at diagnosis of a similar subject who was a tumor case; in other centers, this was the age of the control at the time of selection for the study and the date of selection. Approximately one-third of children with brain tumors for whom vitamin supplement data were available were less than 5 years of age, 54% were male, and 50% had astroglial tumors (Table 1). All of these who had a primary tumor of the brain, cranial nerves or cranial meninges (ICD-O site codes 191, 192.1 and 192.2) were eligible. Further details of control selection and other study design features at each of the participating centers are available from earlier reports from individual centers [7, 9, 23, 26].

The common study questionnaire asked mothers about several exposures she might have had during the index pregnancy, including use of specific medications. The final questions in this section of the questionnaire were about use of vitamin supplements. Mothers were asked specifically about intake of multivitamins and of vitamin C and vitamin E supplements. Detailed data were collected on timing (month before pregnancy, specific trimesters, use during breast feeding), brand or type, frequency, and duration of vitamin supplementation.

At some centers, vitamin use was not queried in the standard manner. In Paris, for example, a mother's use of vitamin supplements was asked about in the section on her diet during pregnancy, so that no information is available on use during the month before pregnancy or while breast feeding. Each center provided micronutrient content for each supplement brand reported. Neither the US centers nor Winnipeg had information on brand names of the supplements used; for US centers, however, specific types of multivitamins taken were queried (e.g., regular, high potency, prenatal). Where type but not specific brand of vitamin was reported, market surveys were conducted to determine average levels of micronutrients in various types of supplements. The percentage of respondents from each center (other than US and Winnipeg) who reported vitamin use but did not report specific brands was 72% in Israel, 67% in Milan, and 57% in Valencia. Micronutrient analyses were restricted to vitamins C, E, and A and folate.

Maximum likelihood estimates of odds ratios OR and 95% confidence intervals (CI) were computed using both conditional and, to minimize the problem of missing data within strata, unconditional logistic regression stratified by center, sex and age group [3]. Five centers (Seattle, Winnipeg, Valencia, Milan, and Israel) also used geographic region as a matching variable. Unconditional risk estimates for Seattle and Winnipeg were also adjusted for geographic region. For the other centers that matched on region (Valencia, Milan, and Israel), there were too many levels of region to allow for ad-

Table 1 Characteristics of cases and controls with maternal vitamin supplementation data available

Characteristic	Cases (n=1051)		Controls (n=1919)	
	n	%	n	%
Age at diagnosis (years) ^a				
<5	372	35	579	30
5–9	315	30	594	31
10–14	227	22	448	23
15–19	137	13	298	16
Male	564	54	1068	56
Year of diagnosis ^a				
1976–1979	3	0.3	6	0.3
1980–1984	167	16	270	14
1985–1989	685	65	1256	65
1990–1994	196	19	387	20
Morphologic subgroup				
Astroglial	529	50	–	–
Primitive neuroectodermal	232	22	–	–
Other glial	282	27	–	–
Unknown	8	1	–	–
Study center				
Paris	67	6	107	6
Milan	80	8	314	16
Valencia	57	5	116	6
Israel	300	29	573	30
Winnipeg	14	1	21	1
Los Angeles	300	29	307	16
San Francisco	101	10	200	10
Seattle	132	13	281	15

^a Varied by study center. For non-US controls, age and year of diagnosis are the age and year of selection. For US controls, age and year are the age at diagnosis of a similar case and the year in which the control attained the case's diagnosis age

justment in unconditional analyses. For individually matched studies, strata for conditional analyses were defined by matched sets; for frequency matched studies, strata were defined by center, sex and age group (0–1, 2–3, 4–5, 6–8, 9–11, 12–14, 15–19 years). Since estimates were similar using both conditional and unconditional methods, only results from unconditional analyses are reported. Birth year, parents' education, and child's use of vitamin supplements were considered as potential confounders. Parents' education was defined as the highest level attained by either parent and was dichotomized for analysis; parents in the upper level had at least some college education. Race was not considered as a confounder because of its homogeneity within each center except Los Angeles (race as a potential confounder in the US data is addressed in the "Discussion" section). Risk estimates and confidence intervals from random effects models (with center as the random effect) are reported for exposure effects that differed by center [8]; otherwise, results from fixed effects models are reported. Other factors considered as possible effect modifiers were gender, birth year, and parents' education. For tumor-specific analyses, cases within each tumor group were compared with all controls; morphologic subgroups were defined as [30]: astroglial (9380–9384, 9400–9421, 9424–9442); PNET (9470–9473; 9501); and all other tumors (8000–8004, 8010, 8800, 8801, 8850, 8900–8910, 8940–8990, 9060–9085, 9150–9161, 9350–9364, 9390–9394, 9450, 9451, 9480, 9490, 9500, 9503–9505, 9530–9538, 9540–9570). A series of analyses restricted to histologically confirmed cases (91% of total) was performed. The length of time between pregnancy and interview was evaluated as a potential source

Table 2 Risk of childhood brain tumor by maternal vitamin supplementation during pregnancy by study center (OR odds ratio, CI confidence interval)

Study center	No. cases (%)	No. controls (%)	OR (95% CI) ^a
Israel	9 (3)	15 (3)	1.2 (0.5, 2.7)
Los Angeles	229 (76)	263 (86)	0.5 (0.3, 0.8)
Milan	17 (21)	65 (21)	1.0 (0.5, 1.9)
Paris	6 (9)	3 (3)	4.3 (0.8, 22.2)
San Francisco	89 (88)	183 (92)	0.7 (0.3, 1.5)
Seattle	116 (88)	249 (89)	1.0 (0.5, 1.8)
Valencia	27 (47)	45 (52)	0.6 (0.3, 1.4)
Winnipeg	3 (27)	7 (33)	0.6 (0.1, 2.8)

^a Adjusted for sex and age group; Seattle and Winnipeg, also adjusted for geographic region

of bias. Multiple logistic regression was used to assess independent effects of multiple exposures. Dose-response trend tests for individual micronutrient intake were performed using log-transformed data; for categorical analyses, unexposed mothers were the reference group and cut-off points were tertiles of exposure among all exposed mothers. Hypothesis testing was two sided, with a significance level of 0.05. Analyses were performed using Epilog Plus statistical software (Vers. 3.99, Epicenter Software, Pasadena, Calif., USA).

Results

Reported use of vitamins during the prenatal period varied considerably by study center. Among control mothers, reported use varied from 3% in Israel and in Paris to 86–92% at the three US centers (Table 2). Intermediate levels of use were reported by control women from the other centers (21% in Milan, 33% in Canada, and 47% in Valencia). A significantly decreased risk of childhood brain tumor associated with any reported use of vitamins during pregnancy was observed in the Los Angeles data (OR=0.5; CI=0.3–0.8, adjusted for age at diagnosis and gender). Decreased risks that did not reach statistical significance were observed in San Francisco, Valencia and Winnipeg. Statistically nonsignificant elevations in risk were observed with data from Israel and Paris, the study centers with the lowest reported levels of vitamin use. The remaining two study centers, Milan and Seattle, had risk estimates of 1.0.

When data for all sites were combined, the risk of brain tumor associated with any maternal prenatal vitamin use, adjusted for age, sex, and study center, was 0.8 (CI=0.6–1.0); with center as a random effect the OR was 1.0 (CI=0.4–2.4), and when data from US centers were excluded the OR was 1.1 (CI=0.7–1.5). Refinement of the exposure period was attempted by computing risk estimates associated with maternal vitamin use during the month prior to the pregnancy (as a surrogate for use during the very early pregnancy), during the pregnancy, and during breast feeding immediately after the child's birth,

Table 3 Risk of childhood brain tumor by exposure period and duration of daily maternal vitamin supplementation during pregnancy

	No. of cases (%)	No. of controls (%)	OR (95% CI) ^a
Exposure period			
Month pre-pregnancy	49 (5)	66 (3)	1.2 (0.8, 1.8)
Pregnancy	496 (47)	839 (44)	0.7 (0.6, 1.0)
Breast feeding	202 (19)	351 (18)	0.9 (0.7, 1.2)
Trimester of exposure			
First	410 (42)	687 (38)	1.0 (0.7, 1.4)
Second	457 (46)	772 (43)	0.8 (0.5, 1.3)
Third	451 (46)	760 (42)	0.9 (0.6, 1.5)
Duration			
Never took daily	579 (56)	1107 (58)	1.0
<2 trimesters	83 (8)	143 (8)	0.8 (0.6, 1.2)
2 trimesters	174 (17)	267 (14)	0.7 (0.5, 0.9)
All 3 trimesters	207 (20)	389 (20)	0.6 (0.5, 0.8)

^a Adjusted for center, sex, and age group; for exposure period and trimester of exposure analyses, each exposure period is also adjusted for the other two

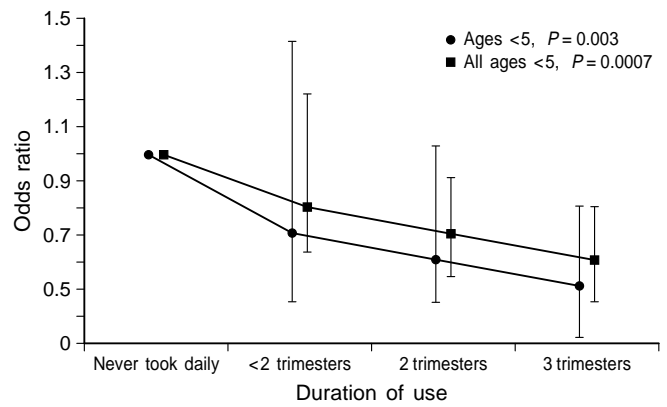
Table 4 Risk of childhood brain tumor by duration of daily maternal vitamin supplementation during pregnancy by morphologic subgroup^a

Duration	No. cases (%)	No. controls (%)	OR (95% CI) ^b
Astroglial			
Never took daily	263 (50)	1107 (58)	1.0
<2 trimesters	43 (8)	144 (8)	0.8 (0.5, 1.3)
2 trimesters	108 (21)	270 (14)	0.8 (0.6, 1.1)
All 3 trimesters	112 (21)	389 (20)	0.6 (0.4, 0.9)
PNET			
Never took daily	138 (60)	1107 (58)	1.0
<2 trimesters	19 (8)	143 (8)	0.8 (0.5, 1.5)
2 trimesters	25 (11)	267 (14)	0.4 (0.2, 0.8)
All 3 trimesters	49 (21)	389 (20)	0.6 (0.4, 1.1)
Other glial			
Never took daily	171 (62)	1107 (58)	1.0
<2 trimesters	20 (7)	143 (8)	0.7 (0.4, 1.2)
2 trimesters	41 (15)	267 (14)	0.6 (0.4, 1.0)
All 3 trimesters	46 (17)	389 (20)	0.5 (0.3, 0.9)

^a All controls were used for each subset of cases

^b Adjusted for center, sex, and age group

with simultaneous adjustment for any use during all periods (Table 3). Mothers could be in none, one, two, or all three of these exposure groups. The results suggest that any decreased risk may be restricted to vitamin use during pregnancy (OR=0.7, CI=0.6–1.0). Relative to women who did not use vitamins during the index pregnancy, decreased risks for childhood brain tumor were observed for those who used vitamins for two trimesters (OR=0.7, CI=0.5–0.9), or throughout all three trimesters (OR=0.6, CI=0.5–0.8, *P* trend=0.0007, Table 3). The suggested decrease in risk of childhood brain tumors with increasing

**Fig. 1** Duration of daily use of prenatal vitamins and risk of childhood brain tumors for children less than 5 years old at diagnosis compared with all children

duration of vitamin use during pregnancy was seen for each of the three major morphologic tumor subtypes: astroglial (*P* trend = 0.009), PNET (*P* trend=0.05), and other glial (*P* trend=0.01; Table 4). This effect was apparent among children of all ages, but was somewhat more marked among children who were less than 5 years of age at diagnosis (Fig. 1). When data from US centers were excluded, there was no trend relating duration of use to risk.

Since most mothers took multivitamin compounds, it is difficult to determine effects of individual micronutrients. Nonetheless, among children who were less than 5 years old at diagnosis, there is a suggestion of a decreasing risk of tumor with increasing daily dose of each of four micronutrients analyzed individually (Table 5). In general there is a progressive reduction of risk across the four levels of exposure for each of the micronutrients (*P* trend=0.01, 0.004, 0.002, and 0.002 for vitamins C, E, and A and folate), but some differences among the various micronutrients are noteworthy. For vitamin C risk reduction is progressive across exposure levels, and risk among those who took at least 100 mg per day is 0.5 (CI=0.3–0.9). For vitamins E and A and for folate, there is a sharp reduction in risk among those who took a small level of daily supplement compared with those who took none. For vitamin E, risk was similarly reduced (OR=0.5) among those in the third (10.3–13.2 mg) and fourth (≥ 13.3 mg) exposure levels of daily use. The highest levels of exposure were 100 mg or more for vitamin C, 13.3 mg or more for vitamin E, 5000 IU or more for vitamin A and 400 μ g or more for folate. Average levels of nutrients contained in supplements reported by each center varied considerably across centers: vitamin C from 67 to 203 mg/dose; vitamin E from 8 to 46 mg/dose; vitamin A from 3738 to 25,000 IU/dose and folate from 100 to 1250 μ m g/dose (Table 6).

While parents' education was not a confounder, reduced brain tumor risk from maternal vitamin supplementation was somewhat more evident among children with more highly educated parents. However, results when education

Table 5 Dose-response for maternal selected micronutrient supplementation during pregnancy for subjects <5 years of age at diagnosis

Daily dosage ^a	No. cases (%)	No. controls (%)	OR (95% CI) ^b
Vitamin C (mg)			
0.0	176 (47)	277 (48)	1.0
<75.9	66 (18)	70 (12)	0.8 (0.5, 1.5)
<100.0	38 (10)	55 (10)	0.6 (0.3, 1.1)
≥100.0	93 (25)	177 (31)	0.5 (0.3, 0.9)
Vitamin E (mg)			
0.0	180 (49)	279 (48)	1.0
<10.3	68 (18)	77 (13)	0.6 (0.3, 1.1)
<13.3	28 (8)	44 (8)	0.5 (0.2, 1.0)
≥13.3	95 (26)	176 (31)	0.5 (0.3, 0.8)
Vitamin A (IU)			
0	180 (49)	277 (48)	1.0
<3900	61 (16)	77 (13)	0.6 (0.3, 1.0)
<5000	33 (9)	41 (7)	0.6 (0.3, 1.2)
≥5000	97 (26)	181 (31)	0.4 (0.2, 0.8)
Folate (μg)			
0	180 (49)	277 (48)	1.0
<313	65 (18)	78 (14)	0.6 (0.3, 1.1)
<400	34 (9)	40 (7)	0.6 (0.3, 1.3)
≥400	92 (25)	179 (31)	0.5 (0.3, 0.8)

^a Exposure categories are mutually exclusive

^b Adjusted for center, sex, and age group. Risk estimates are not adjusted for other micronutrients listed

Table 6 International variation in micronutrient content of vitamin supplements

Center	Average micronutrient content ^a			
	Vit C (mg)	Vit E (mg)	Vit A (IU)	Folate (μg)
Paris	325	20	25000	250
Milan	128	46	14300	100
Valencia	67	8	3738	333
Israel	162	40	5750	1250
Winnipeg ^b	175	40	5000	400
U.S. ^c	203	23	4500	380

^a Of vitamin brands/types reported that contain that micronutrient

^b Specific brands/types not reported; micronutrient content based on typical vitamin for the geographical area

^c Los Angeles, San Francisco, and Seattle

was dichotomized were generally consistent with each other. For example, results of dose-response analyses of the four micronutrients stratified by education level were essentially the same. Risk estimates were unchanged after adjustment for children's use of vitamin supplements. Among controls, prevalence of vitamin supplement use during pregnancy gradually increased over time, from 49% in the birth years 1965–1969 to 57% for birth years 1985 and later, and risk estimates were generally lower among subjects born in 1980 or later (though birth year was not a confounder). Risk estimates were similar for each gender

and also did not differ by histological confirmation. Interview quality was considered as a potential source of bias; however only 6.5% of all interviews were deemed “questionable” or “unsatisfactory” by the interviewer.

Discussion

Intake of vitamin supplements during pregnancy was associated with an apparent reduction of risk in earlier studies [4, 5, 25, 26, 29] and in this largest case-control study of childhood brain tumors to date. Risk reduction appeared to relate only to use during pregnancy rather than use during the month before pregnancy or during breast feeding, and the greatest risk reduction was observed when vitamins were taken during the entire pregnancy. The reduction of risk was greatest among children diagnosed at younger ages (<5 years at diagnosis), but also was seen among older children.

This international study has a number of limitations that must be considered. The small number of cases in most centers (<100 cases in all but the US and Israeli studies) and the low prevalence of vitamin use in some geographic areas (e.g., 3% among control mothers in Israel and in Paris) resulted in varied center-specific risk estimates and combined risk estimates that were dominated by findings in the US, where vitamins were taken by the majority of mothers; in fact, the non-US data added only a 14% increase in number of exposed cases and a 19% increase in number of exposed controls, despite 126% and 178% increases in total numbers of cases and controls, respectively. This may suggest that the US findings are the result of an unknown confounder, such as quality of prenatal care, that is related to reduced brain tumor risk, or that vitamin compounds in the US differ in ways that make them more effective in reducing risk. Although supplements used in all geographic areas contained at least some of each of the four micronutrients, average levels of nutrients contained in supplements reported by each center varied considerably across centers, as indicated in Table 6.

There is a suggestion that an increasing reduction in risk occurs with increasing daily intake of each micronutrient evaluated (vitamins C, E, and A and folate), but because most mothers took a multivitamin compound, intake of these four was highly correlated. In addition, specific brand names of vitamins taken were not known or not recorded for many mothers (though US centers asked about specific types of multivitamins taken). As in any retrospective case-control study, the possible influence of recall bias is a concern. We did not have the necessary data to perform a validation analysis against medical records. However, in studies of childhood cancer, recall bias is usually associated with case mothers trying harder than control mothers to remember medication use and other exposures during the index pregnancy. If such bias is present in relation to an ap-

parently protective exposure such as vitamin use, it would have had the effect of biasing our risk estimates toward the null. Further, there is some evidence to suggest that recall bias does not exist in studies of adverse reproductive outcomes that use mothers as respondents [17]. Though the lower risk estimates we observed for later birth years may be due to increasing prevalence of supplementation over time, they may also suggest nondifferential poor recall among mothers whose pregnancies were in the distant past.

In the US portion of the study, findings relating to vitamin use remained after controlling for all factors considered in the pooled analysis as well as mother's education, social class (an index considering education and occupation of head of household), ethnicity (Latino, other white, black and other), and mother's diet during pregnancy [26]. The US data were also evaluated with respect to whether or not pregnancies were planned, which did not confound the US results. It is possible that respondents differed from nonrespondents in these factors or in the exposures we studied (although participation rates at the US centers were around 70% or higher), or that controls targeted for participation (through random digit dialing) were not representative of the population. However, these potential biases are not quantifiable in this study. We are processing the dietary data from each center to allow a combined analysis of micronutrient intake from diet and supplements, which will be particularly useful for centers in which prevalence of supplementation was low (e.g., Israel and France) and thus a minor contributor to population intake of micronutrients. The dietary analysis will also allow us to examine the modifying effects of supplement intake in relationship to other dietary constituents such as nitrite from cured meats, an important consideration because both vitamins C and E are effective inhibitors of nitrosation, as described below. However, the dietary data from this study have their own set of limitations. The focus of this study was investigation of the *N*-nitroso hypothesis. Therefore, the questionnaire asked only about those 40–50 foods that account for 90% of population intake of nitrite, nitrate, and vitamins C and E in each geographic area under study [12]. The list of foods queried varies considerably across centers. In addition, these lists were not designed to assess intake of most micronutrients (e.g., folate and vitamin A) or of macronutrients (e.g., fat or animal protein). The Israel study is an exception, however, in that relatively complete dietary data (i.e., not just on foods most closely correlated with intake of nitrite, nitrate, and vitamins C and E) were collected.

Our data suggest an increasing use of prenatal vitamin supplements over time, which is inconsistent with the modest increase in the US incidence of pediatric brain tumors over the past 20 years [11]. However, the increased incidence is probably due to the simultaneous effects of several different factors, such as improved diagnosis and possible secular changes in environmental exposures that may increase risk. The effects of these potential influences on

pediatric brain tumor incidence cannot be disentangled when comparing the trends in incidence and prevalence of this single exposure.

Nitrite from cured meats is an important precursor of carcinogenic *N*-nitroso compounds commonly formed in the gut after ingestion of precursor compounds [18, 21]. One group of these compounds, the nitrosoureas, has been shown to cause nervous system tumors in experimental animals [13–16, 28]. When exposure is transplacental, only low doses of precursors such as sodium nitrite and ethyl urea in the food and drinking water of the pregnant rats are required for 100% tumor induction in offspring; this effect can be blocked if ascorbate (vitamin C) and/or alpha tocopherol (vitamin E) are added to the dams' diet [20]. In the US portion of this study, we found risk of brain tumors to be substantially higher for children of mothers who consumed above-average quantities of cured meats during their pregnancies and did not take vitamins compared with than for those of mothers who did take vitamins [26]. This synergism also was seen in a small earlier study [29]. The hypothesis that childhood brain tumors relate to maternal exposure to *N*-nitroso compounds during the pregnancy was the primary focus of this international study.

Various possible mechanisms have been suggested by which vitamin and mineral supplementation may reduce cancer risk [22]. Antioxidants (e.g., vitamins C and E) can prevent oxidative damage to DNA by scavenging free radicals [10]. Some micronutrients, such as vitamins A and D, have been shown to have a role in cell differentiation and proliferation [2]. Supplementation may prevent deficiencies, such as folic acid deficiency, which may lead to malignant transformation of normal cells by weakening chromosomal structure and altering gene expression [6]. Presence of micronutrients in the gut or bladder can prevent endogenous formation of carcinogens (such as *N*-nitroso compounds) or alter metabolism of mutagens. It is possible that the developing brain may be more susceptible to some of these effects because of the higher rate of brain cell proliferation during gestation and early childhood and the fetal brain's lower ability to rid itself of mutagenic compounds [27].

Our findings of a huge variation in prevalence of use of prenatal vitamins and of the content of vitamin compounds across countries may be of interest to clinicians and public health workers. In addition, we hope that our findings will stimulate investigators to consider vitamin supplementation in future epidemiologic studies of childhood brain tumors and of other pediatric cancers.

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