

Maternal prenatal exposure to nitrosatable drugs and childhood brain tumours

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Background A compelling hypothesis was proposed that childhood brain tumours are associated with maternal exposure to N-nitroso compounds during the prenatal period. Many common drugs, such as antihistamines, aspirin, and antibiotics, are nitrosatable and depending upon the product, potentially carcinogenic. We hypothesized that maternal ingestion of certain subgroups of nitrosatable drug products during pregnancy increases the risk of brain tumour development in offspring.

Methods Data were collected as part of a population-based case-control study of childhood brain tumours and mothers' self-reported exposure to therapeutic drugs and dietary nitrites. Cases were enrolled from three US West Coast SEER tumour registries: Seattle-Puget sound, Los Angeles County, and the San Francisco-Oakland Bay Area. Tumours were grouped into three major histological tumour subtypes: astroglial, primitive neural ectodermal tumours, and all remaining glial tumours ('other glial'). Therapeutic drugs reported by mothers were translated into active chemical compounds and classified as secondary amines, tertiary amines, amides, or none of the three. Risk estimates were computed according to classes of nitrosatability, potential carcinogenicity, teratogenicity, and predicted end product.

Results We found no significant association between maternal use of nitrosatable drugs, either overall or within any of the nitrosatable drug classifications, and subsequent development of brain tumours in children. Nitrite consumption from cured meats was not an effect modifier. However, exposure to nitrosoephedrine during pregnancy was associated with significantly increased risk of 'other glial' tumours (OR = 3.1; 95% CI: 1.1–9.2).

Conclusions These findings do not support an association between maternal use of nitrosatable drugs during pregnancy and brain tumour risk in offspring. While exposure to the nitrosation end product nitrosoephedrine was associated with increased risk for other glial tumours, the finding was not specific to any one type of tumour.

Keywords Child, brain tumour, nitrite, drug, N-nitroso compound, amine, amide, carcinogenic, epidemiology

After years of epidemiological and experimental research, ionizing radiation remains the only established cause of childhood brain

tumours. However, a compelling hypothesis persists that childhood brain tumours are associated with maternal exposure to N-nitroso compounds (NOC) during the prenatal period.¹ The NOC are a group of potentially carcinogenic chemical compounds that includes nitrosamines (R₁NNOR₂) and nitrosamides (R₁NNO.COR₂).² Endogenous formation of NOC in the maternal stomach and the subsequent transplacental transmission to the fetus is the most likely source of significant prenatal exposure to these agents. Experimental studies show that both nitrosamides and nitrosamines can be formed *in vivo* from their chemical precursors (amides, amines, and nitrites) under normal acidic conditions of the stomach³ and that a single transplacental dose

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of ethylnitrosourea (a type of nitrosamide) is sufficient to induce central and peripheral nervous system tumours in 100% of the offspring.⁴ Some therapeutic drugs provide a concentrated source of amides or amines which, in the presence of nitrites in the stomach from the diet or in the saliva, can be nitrosated to form NOC.⁵ These products may act locally or circulate in the bloodstream to act in distant tissues, including the central nervous system.^{4,6,7} Many common drugs such as antihistamines, aspirin, and antibiotics are nitrosatable and, depending on the product, potentially carcinogenic.⁸

Of the many nitrosatable therapeutic drugs, those that are amides or tertiary amines are most likely to form potent carcinogens. Nitrosamides, specifically the nitrosocarbamates and nitrosoureas, consistently have been shown to act as neurocarcinogens in experimental studies of rats, mice, rabbits, opossums, and patas monkeys.^{9,10} Nitrosatable secondary and tertiary amines have not been associated with nervous system tumours in animal models. However, they are known to produce carcinogenic derivatives associated with tumours in many tissues, such as liver, stomach, and oesophagus. Secondary amines typically result in weak or non-carcinogenic derivatives, whereas tertiary amines result in strong carcinogens of low molecular weight.¹¹

N-nitroso compounds are rarely present in the environment in significant quantities, but NOC precursors such as nitrites, amides, and amines are common. For example, digestion of cured meats results in a concentrated source of nitrites in the stomach that has been associated with increased risk of childhood brain tumours in our data and in previous studies.^{1,12–14} Nitrite is usually present in saliva from bacterial reduction of dietary nitrate.¹⁵ Both prescription and over-the-counter drugs can be sources of nitrosatable amides or amines. Although nitrosatable drugs have been associated with childhood tumours in general,¹⁶ a study of childhood brain tumours that did not account for the different types of amino compounds found no association.¹⁷

Our purpose was to evaluate whether maternal ingestion of certain subgroups of nitrosatable drug products during pregnancy, namely drugs that are amides or tertiary amines, either alone or in combination with dietary nitrites, increase the risk of brain tumours in offspring. Here we present the results from a population-based case-control study of childhood brain tumours and mothers' self-reported exposure to therapeutic drugs and dietary nitrites.

Methods

Data were collected as part of a multi-centre, population-based, case-control study to examine the relationship between childhood brain tumours and potential exposures to NOC through diet, employment, and lifestyle factors. Cases were enrolled from three US West Coast Surveillance Epidemiology and End Results (SEER) tumour registries: Seattle-Puget Sound, Los Angeles County, and the San Francisco-Oakland Bay Area. Eligible cases were ≤ 19 years of age at diagnosis of a primary brain tumour from January 1984 through December 1990 (Seattle and San Francisco) or August 1991 (Los Angeles). Case diagnoses included primary tumours of the brain, cranial nerves, or cranial meninges of any histological type (International Classification of Diseases-Oncology [ICD-O] codes 191, 192.0, 192.1).¹⁸ A total of 813 cases were identified from the three tumour registries

during the study period. Of these cases, 762 (94%) met eligibility requirements to be included in the study. A total of 540 (71%) of the eligible mothers completed interviews. The non-participating cases consisted of 106 families (14%) who were not traceable, 73 cases (10%) who refused to participate in the study after being contacted, 23 (3%) whose physician refused permission to contact the family, 12 (2%) who were untraceable, and 8 (1%) who did not participate for other reasons. Controls were selected using a two-stage random digit dialling procedure and were frequency matched to cases, within study sites, on gender and birth year.¹⁹ Controls were assigned a reference age equal to the diagnosis age of a similar case. The interview response rate for all residents who initially screened eligible was 74% (801/1079). Detailed methods have been published previously.^{13,20}

Cases were grouped into three major histological tumour subtypes described by Rorke:²¹ astroglial (morphology codes 9380–9384, 9400–9421, 9424–9442); primitive neural ectodermal tumours (PNET; morphology codes 9362, 9470–9473, and 9500); and all remaining tumours, which were a mix of several histological types of glial tumours (morphology codes 8000, 8002, 8800, 9064, 9071, 9080, 9084, 9150, 9161, 9390–9392, 9450, 9451, 9463, 9490, 9501, 9505, 9530, 9532, 9538, 9560, 9861, 9990).

Information was collected through in-person interviews with all mothers and 77% of fathers, using in-person or telephone interviews. Mothers' interviews lasted approximately an hour and a half and included questions on demographics, medical history of children and parents, smoking history, diet, household products, occupation of both parents, and therapeutic drugs. Mothers were interviewed in person to determine a complete list of therapeutic drugs (prescription and non-prescription) that they used in the year preceding their pregnancy, during their pregnancy (by trimester), and while breastfeeding the index child. Mothers were asked to recall whether they ever used a specific category of drug during their pregnancy (e.g. antihistamines) and, if so, the specific drug and/or brand name of the drug. Cards containing lists of product names and colour pictures of common drugs were available as recall aids.

Therapeutic drugs reported by mothers were translated into active chemical compounds.^{22,23} Each chemical compound was classified by a chemist (WL) as a secondary amine, tertiary amine, amide, or none of the three. Amines and amides were further classified (by WL) according to nitrosatability based on published experimental data or chemical structure and by probable end products (e.g. nitrosopyrrolidine). Nitrosatable drugs were further classified (by WL) by carcinogenicity based on chemical structure, published experimental data, and/or carcinogenicity of their probable end products. Finally, chemicals were classified in terms of teratogenicity using the Catalog of Teratogenic Agents.²⁴

Maximum likelihood estimates of odds ratios (OR) and 95% CI were computed using unconditional logistic regression adjusted for age at diagnosis (≤ 1 , 2–3, 4–5, 6–8, 9–11, 12–14, 15–19), gender, year of birth (1965–1969, 1970–1974, 1975–1979, 1980–1984, 1985–1990) and study site. Analyses were performed for all cases combined and by major histological subgroup. For each subgroup-specific analysis, all controls were used as the comparison group. The following were considered as potential confounders, but were not included in the final results because

they did not appreciably affect risk estimates: parents' race (white, African American, Hispanic, Asian/other), parents' socioeconomic status (a continuous measure based on education and occupation²⁵), mother's age at pregnancy (continuous), mother's use of vitamin supplementation during pregnancy (dichotomous), and mother's intake of nitrite from cured meats during pregnancy (continuous). Method of estimation of nitrite intake for each mother has been previously detailed.¹³ Nitrite intake also was considered as a dichotomous effect modifier with a cutpoint of 0.0705 mg/day, which was the median intake level among all subjects. Effect modification was further evaluated by categories of socioeconomic status (a categorical measure based on education and occupation; lower ≥ 40 , higher < 40 ²⁵), vitamin supplementation, trimester of exposure, and age of diagnosis (< 5 years of age, ≥ 5 years of age).

Results

The study included 540 eligible cases and 801 controls. In all, 308 cases (57%) were diagnosed as astroglial tumour, 109 (20%) as PNET, and the remaining 123 as other glial tumour. Approximately 55% of cases were male and 35% were under the age of 5 years (Table 1). The majority of case and control participants were white (58% and 67%, respectively) or Latino (27% and 23%), with small numbers of African-American

(8% and 5%), Asian (5% and 4%), and other races/ethnicities (2% and 2%).

For both case and control mothers, 17% reported having taken a nitrosatable drug during pregnancy (Table 2) and 20% reported to have taken a nitrosatable drug during pregnancy or while breastfeeding. There were no significant associations between maternal use of nitrosatable drugs, either overall or within any of the nitrosatable drug classifications, and subsequent development of brain tumours in children (Table 2); nor were there any significant associations by major histological tumour subtypes (Table 3). Teratogenic drugs were not associated with increased risk of brain tumour, either overall or by histological subtype (Tables 2 and 3).

There were no associations with brain tumour risk for any predicted end product of nitrosation (Table 4). For the two end products with the highest prevalence of exposure, nitrosoephedrine and nitrosodimethylamine, we performed additional analyses by trimester of exposure (first, second, third), dose (0, 0.1–150, ≥ 150 mg), and histological subtype (astroglial, PNET, other glial) (data not shown). Use of nitrosoephedrine during pregnancy was associated with significantly increased risk of 'other glial' tumours (OR = 3.1; 95% CI: 1.1–9.2), but the finding was not specific to any one type of tumour (6 exposed cases = 2 ependymomas, 1 ganglioma, 1 oligodendroglioma, 1 germinoma, and 1 glial tumor that was not microscopically confirmed). Risk was higher in the first trimester (OR₁ = 1.5; 95% CI: 0.5–4.8) than the second and third trimesters (OR₂ = 1.2; 95% CI: 0.4–3.8); OR₃ = 0.9; 95% CI: 0.3–3.4), but the trend was not significant. No other significant associations were found for the additional nitrosoephedrine and nitrosodimethylamine analyses.

Further stratified analyses were completed by age (all ages of diagnosis and diagnosis < 5 years) and maternal intake of nitrite from cured meats during pregnancy (low intake ≤ 0.0705 mg/day which was the median intake level among all subjects and high intake > 0.0705 mg/day) (data not shown). We found no increase in risk for mothers who used nitrosatable drugs during

Table 1 Gender, age, ethnicity, socioeconomic status (SES), and area of residence of childhood brain tumour cases and controls, US West Coast Childhood Brain Tumor Study, 1984–1991

Characteristics	Cases		Controls	
	No.	%	No.	%
Gender				
Males	298	55	448	56
Females	242	45	353	44
Age^a (years)				
≤ 4	188	35	287	36
5–9	158	29	232	29
10–19	194	36	282	35
Race/ethnicity^b				
White	313	58	532	67
Latino	147	27	183	23
African American	42	8	41	5
Other	38	7	44	6
SES^c				
Lower	314	58	373	47
Higher	226	42	427	53
Residence				
Los Angeles	304	56	315	39
San Francisco	102	19	205	26
Seattle	134	25	281	35
Tumour type				
Astroglial	308	57		
Medulloblastoma or PNET ^d	107	20		
Other glial	125	23		
Total	540		801	

^a Age of diagnosis for cases, reference age for controls.

^b One control had missing race.

^c Based on the parents' education and occupation, according to the Hollingshead Social Index;²⁵ lower ≥ 40 , higher < 40 .

^d Primitive neuroectodermal tumour.

Table 2 Maternal exposure to nitrosatable amine and amide drugs during pregnancy, US West Coast Childhood Brain Tumor Study, 1984–1991

Drug	No. cases (%)	No. controls (%)	OR ^c (95% CI)
Amines & amides			
Nitrosatable ^a	87 (17)	127 (17)	1.1 (0.8–1.5)
Nitrosatable & carcinogenic ^b	63 (12)	89 (12)	1.1 (0.8–1.6)
Secondary amines			
Nitrosatable ^a	47 (9)	70 (9)	1.0 (0.7–1.5)
Nitrosatable & carcinogenic ^b	21 (4)	24 (3)	1.4 (0.7–2.5)
Tertiary amines			
Nitrosatable ^a	72 (14)	102 (13)	1.1 (0.8–1.5)
Nitrosatable & carcinogenic ^b	58 (11)	79 (10)	1.1 (0.8–1.6)
Any type of amides	7 (1)	23 (3)	0.5 (0.2–1.2)
Teratogens	31 (6)	45 (6)	1.0 (0.6–1.7)

^a Based on published data and chemical structure.

^b Drugs that are likely to be carcinogenic, as well as nitrosatable, based on published data and chemical structure.

^c Adjusted for age of child at diagnosis, gender, year of birth, and geographical location.

Table 3 Maternal exposure to nitrosatable amine and amide drugs during pregnancy by histological type, US West Coast Childhood Brain Tumor Study, 1984–1991

Tumour type	Drug	No. cases (%)	No. controls (%)	OR ^c (95% CI)
Astroglial	Amines & amides			
	Nitrosatable ^a	50 (17)	127 (17)	1.1 (0.7–1.5)
	Nitrosatable & carcinogenic ^b	37 (13)	89 (12)	1.1 (0.7–1.7)
	Secondary amines			
	Nitrosatable ^a	28 (10)	70 (9)	1.1 (0.7–1.8)
	Nitrosatable & carcinogenic ^b	13 (4)	24 (3)	1.5 (0.7–3.0)
	Tertiary amines			
	Nitrosatable ^a	40 (13)	103 (13)	1.0 (0.7–1.5)
	Nitrosatable & carcinogenic ^b	32 (11)	9 (10)	1.0 (0.6–1.6)
	Any type of amides	8 (3)	23 (3)	0.9 (0.4–2.2)
PNET ^d	Teratogens	17 (6)	45 (6)	1.0 (0.6–1.8)
	Amines & amides			
	Nitrosatable ^a	16 (15)	127 (17)	1.0 (0.6–1.8)
	Nitrosatable & carcinogenic ^b	12 (11)	89 (12)	1.1 (0.6–2.1)
	Secondary amines			
	Nitrosatable ^a	5 (5)	70 (9)	0.5 (0.2–1.3)
	Nitrosatable & carcinogenic ^b	0 (0)	24 (3)	–
	Tertiary amines			
	Nitrosatable ^a	14 (13)	102 (13)	1.2 (0.6–2.2)
	Nitrosatable & carcinogenic ^b	12 (11)	79 (10)	1.2 (0.6–2.5)
Any type of amides	0 (0)	23 (3)	–	
Other Glial	Teratogens	7 (7)	45 (6)	1.2 (0.5–2.9)
	Amines & amides			
	Nitrosatable ^a	21 (18)	127 (17)	1.3 (0.7–2.1)
	Nitrosatable & carcinogenic ^b	14 (12)	89 (12)	1.1 (0.6–2.1)
	Secondary amines			
	Nitrosatable ^a	14 (12)	70 (9)	1.4 (0.8–2.7)
	Nitrosatable & carcinogenic ^b	8 (7)	27 (4)	2.2 (0.9–5.3)
	Tertiary amines			
	Nitrosatable ^a	18 (15)	102 (13)	1.4 (0.8–2.4)
	Nitrosatable & carcinogenic ^b	14 (12)	79 (10)	1.3 (0.7–2.5)
Any type of amides	1 (1)	23 (3)	0.3 (0.0–2.5)	
	Teratogens	7 (6)	45 (6)	1.0 (0.4–2.4)

^a Based on published data and chemical structure.

^b Drugs that are likely carcinogenic, as well as nitrosatable, based on published data and chemical structure.

^c Adjusted for age of child at diagnosis, gender, year of birth, and geographical location.

^d Primitive neural ectodermal tumours.

Table 4 Maternal exposure to drug nitrosation products (derivatives) during pregnancy, US West Coast Childhood Brain Tumor Study, 1984–1991

Nitrosation product ^a	No. cases (%)	No. controls (%)	OR ^b (95% CI)
Nitroschlorothiazior	2 (0.4)	5 (0.6)	0.8 (0.1–4.1)
Nitroschloridiazepoxide	1 (0.2)	1 (0.1)	2.1 (0.1–34.2)
Nitrosotrichlormethazide	1 (0.2)	0 (0.0)	–
Nitrosopyrrolidine	8 (1.5)	5 (0.6)	2.2 (0.7–6.9)
Nitrosomethylcinnamylamine	2 (0.4)	0 (0.0)	–
Nitrosoisometheptene	0 (0.0)	0 (0.0)	–
Nitrosohydrochlorothiazide	2 (0.4)	4 (0.5)	0.9 (0.2–5.3)
Nitrosoepinephrine	1 (0.2)	1 (0.1)	1.7 (0.1–27.8)
Nitrosoephedrine	11 (2.1)	12 (1.5)	1.3 (0.6–3.0)
Nitrosodimethylamine	48 (9.3)	72 (9.2)	1.0 (0.7–1.5)
Nitrosodiethylamine	4 (0.7)	0 (0.0)	–
Nitroso aza bicyclo octanol	1 (0.2)	1 (0.1)	1.0 (0.1–17.0)
Dinitrosopiperazine	1 (0.2)	5 (0.6)	0.4 (0.0–3.3)

^a Most likely nitrosation product based on published data or chemical structure.

^b Adjusted for age of child at diagnosis, gender, year of birth, and geographical location.

pregnancy, regardless of the level of nitrite consumption they reported ($OR_{LOW\ Nitrite} = 1.1$, $OR_{HIGH\ Nitrite} = 1.1$). Similarly, there was no elevation in risk for secondary amines, tertiary amines, or amides by level of dietary nitrite consumption. For children diagnosed before 5 years of age, we found a non-significant increase in risk for tertiary amines, but risk did not increase with increasing dietary nitrite intake ($OR_{LOW\ Nitrite} = 2.1$, $OR_{HIGH\ Nitrite} = 1.3$). Risk was not elevated for use of secondary amines or amides for children diagnosed before age 5 (data not shown).

Discussion

In this study, risk of childhood brain tumours was not increased due to mothers' use of nitrosatable over-the-counter or prescription therapeutic drugs. A previous study of maternal nitrosatable drug use during pregnancy and fetal birth defects found an increased relative risk (RR) for any type of childhood tumour (RR = 2.9; 95% CI: 0.99–5.26) and for major malformations (RR = 1.33; 95% CI: 1.11–1.58) for exposure during the first 4 months of pregnancy.¹⁶ A subsequent case-control study of nitrosatable drugs during pregnancy and childhood brain tumours found no overall increase in risk (OR = 1.15; 95% CI: 0.69–1.94) and no histology-specific increase in risk.¹⁷ While our results of no association agree with these findings, the studies are not directly comparable because the earlier work did not distinguish between nitrosatable amines and amides, which experimental data suggest have very different carcinogenic effects on specific tissues. They also did not chemically subclassify nitrosatable drugs into those likely to form innocuous compounds versus those likely to form potentially carcinogenic ones.

Risk was increased in our data for 'other glial' (i.e. other than astroglial or PNET) tumours among children whose mothers took drugs with the nitrosation end product of nitrosoephedrine. Nitrosoephedrine can result from the nitrosation of pseudoephedrine, an ingredient found in several common over-the-counter decongestants. Its product is a nitrosamine that has been shown to cause tumours of the liver, lung, and forestomach in rats when administered orally^{26,27} but has not been associated with nervous system tumours in animal models. Although our nitrosoephedrine finding was statistically significant, the finding was not specific to one histological type of tumour.

We previously found¹³ a dose–response relationship between cured meat consumption by mothers during pregnancy and risk of childhood brain tumours. In these data, we observed non-significantly increased risks of brain tumours in younger children (≤ 5 years) whose mothers used drugs containing nitrosatable tertiary amines and consumed low levels of cured meat products. No association was found for drugs containing secondary amines or amides. Although the nitrosation products of drugs containing tertiary amino groups are frequently strong carcinogens, their end products have been associated with tumours of sites other than the brain (e.g. liver, oesophagus, nasal and oral cavities, kidney, pancreas, urinary bladder, lung, and thyroid).² Nitrosamides, on-the-other-hand, have been associated with tumours of the nervous system in several animal models, but interestingly were not associated with brain tumour risk in this study. Although the absence of an association in these data may suggest that maternal use of amide-containing

drugs is not a risk factor for childhood brain tumours, the timing of intake of nitrite in relation to drug intake is unknown. It also is unknown whether the quantity of nitrosamide formed was sufficient to be carcinogenic. Further, the specific end product formed and the timing of the exposure in relation to fetal development are also determinants of risk that we could not adequately explore in relation to amide consumption due to small numbers of exposed subjects.

We attempted to examine the association between common nitrosation end products (nitrosoephedrine, nitrosodimethylamine) and the timing of exposure (i.e. trimester of exposure) during the pregnancy. Druckrey²⁸ first reported that transplacental exposure of fetal rats to ethylnitrosourea (ENU) caused neuroepithelial tumours for exposures on or after day 12 of gestation, while exposures on days 5–11 resulted in fetal malformations.^{28,29} Some NOC have both teratogenic and carcinogenic effects depending on the time of gestational exposure and the dose of chemical, while others are weak teratogens, if at all.³⁰ The suggestion of a trend in our data of greatest risk for exposure to ephedrine in the first trimester is consistent with animal studies in which the effect in offspring occurred during early gestation. However, the difference between number of exposed in the first versus second trimester was very small.

We hypothesized that gastric nitrosation would most likely occur among mothers consuming both nitrites (e.g. from cured meats) and amino substrates (from drugs). However, we did not have data on whether these products were consumed at the same time. Consumption would not have had to occur at the same meal, but within a few hours of each other, i.e. while the products were still being digested in the stomach. During gastric nitrosation, nitrite (or nitrous acid) reacts with a nucleophilic catalysts in the stomach (Y^- e.g. NO_2^- , Cl^-) to form nitrosating agents ($Y-NO$) that then may act directly with amines or amides present in the stomach.³¹ N-nitroso compound formation is accelerated principally by raising the concentration of nitrosating agents, but also is dependent on pH, basicity of the amino substrate, presence of catalytic anions (Y^-), and inhibitors.³¹ In general, the rate of the reaction is proportional to the square of the nitrite concentration for secondary and tertiary amines and directly proportional to the nitrite concentration for amides. In both types of reactions, nitrite is the expected limiting factor, while the amine/amide is in excess. Often there is as much as 60 mg of amine/amide per drug, whereas there might be 10 mg of nitrite in food that is consumed during a meal.

Prescription and over-the-counter therapeutic drugs represent a potentially important source of nitrosatable amines and amides because of the large quantities of drugs that people consume.³² It is estimated that cured meats, one of the most concentrated sources of dietary nitrite, account for 39% of total dietary nitrites. Vegetables supply as much as 16% of dietary nitrite, however they also may contain inhibitors of nitrosation such as vitamins C and E.³³ Other sources of preformed NOC and their precursors (nitrites and amines) exist, however these are not as likely to result in a concentrated exposure and were not independent risk factors for brain tumour in our data.

It is possible that mothers of case children may have been more likely than mothers of control children to report therapeutic drug use during pregnancy, but it is unlikely that recall bias would operate within categories of nitrosatability or carcinogenicity. A second concern in case-control studies is whether

participants can accurately recall exposures that occurred years in the past. In this study, we did not validate self-reported exposures to drugs; however, we did examine reliability of reporting by mothers compared with fathers for several questionnaire variables (race, education, smoking history, occupational history). We found that mothers and fathers were able to reliably report the same information on exposures years in the past (smoking, occupation) when questions were restricted to a limited time period (in this case it was the month before and the months during the pregnancy of the child enrolled in the study).³⁴

Our sole finding of increased risk from nitrosatable drugs was observed for tertiary amines and 'other glial' tumours. Nitrosamides, which have been potent neurocarcinogens in animal studies, did not appear to be associated with brain tumour risk in this study, although the number of exposed subjects was small. These data provide little evidence that women who take nitrosatable drugs during pregnancy increase the risk of subsequent brain tumors in their children.

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KEY MESSAGES

- A compelling hypothesis was proposed that childhood brain tumours are associated with maternal exposure to N-nitroso compounds during the prenatal period.
- Many common drugs, such as antihistamines, aspirin, and antibiotics, are nitrosatable and depending upon the product, potentially carcinogenic.
- We hypothesized that maternal ingestion of certain subgroups of nitrosatable drug products during pregnancy increase the risk of brain tumour development in offspring.
- No significant association was found between maternal use of nitrosatable drugs, either overall or within any of the nitrosatable drug classifications, and subsequent development of brain tumours in children.
- Exposure to nitrosoephedrine during pregnancy was associated with significantly increased risk of 'other glial' tumours (OR = 3.1; 95% CI: 1.1-9.2).

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