Maternal Consumption of Cured Meats and Vitamins in Relation to Pediatric Brain Tumors


Department of Preventive Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California 90033-0800 [S. P. M.]; Statology, South Lake Tahoe, California 96150 [J. M. P.]; Fred Hutchinson Cancer Research Center and Department of Epidemiology, University of Washington, Seattle, Washington 98104 [B. A. M.]; Department of Epidemiology and Biostatistics [E. A. H.] and Neuropathology Unit [R. L. D.], University of California, San Francisco, California 94143; and Columbia, Maryland 21044 [W. L.]

Abstract

Brain tumors are the leading cause of death from childhood cancer, yet the causes of most of these tumors remain obscure. Few chemicals are effective in causing brain tumors experimentally after systemic administration of low doses; a notable exception is one group of N-nitroso compounds, the nitrosamides (in particular the nitrosoureas). Feeding pregnant animals nitrosamide precursors (e.g., sodium nitrite and an alkylamide such as ethylurea) causes a high incidence of nervous system tumors in offspring. This population-based epidemiological study was designed to test the hypothesis that maternal consumption during pregnancy of meats cured with sodium nitrite increases the risk of brain tumors among offspring. The intake of vitamins C and E blocks endogenous formation of nitrosamides and was expected to be protective. Mothers of 540 children under age 20 with a primary brain tumor diagnosed during 1984-1991 and 801 control children in the same 19 counties on the U.S. West Coast were interviewed. Risk increased with increasing frequency of eating processed meats (odds ratio (OR) = 2.1 for eating at least twice a day compared to not eating; 95% confidence interval (CI) = 1.3-3.2; P = 0.003). Risk also increased with increasing average daily grams of cured meats or mg of nitrite from cured meats (P for each <0.005) but not with nitrate from vegetables. Daily use of prenatal vitamins throughout the pregnancy decreased risk (OR = 0.54; CI = 0.39-0.75). Risk among mothers who consumed above the median level of nitrite from cured meat was greater if vitamins were not taken (OR = 2.4; CI = 1.4-3.6) than if they were (OR = 1.3). These effects were evident for each of three major histological types and across social classes, age groups, and geographic areas. This largest study to date of maternal diet and childhood brain tumors suggests that exposure during gestation to endogenously formed nitrosamine compounds may be associated with tumor occurrence. Laboratory exploration is needed to: (a) define dietary sources of exposure to alkylamides; (b) investigate the reactivity of nitrite in high concentration such as around bits of cured meats in the stomach after ingestion compared to nitrite in dilute solution; and (c) confirm that simultaneous ingestion of alkylamides and cured meats leads to the endogenous formation of nitrosamides.

Introduction

Brain tumors are the most common solid tumor in children and the most common cause of death from pediatric cancer (1). Inherited syndromes that predispose to brain tumor development such as neurofibromatosis are present in fewer than 5% of patients (2). Ionizing radiation, the only established environmental cause, similarly accounts for no more than a few percent of cases (3).

Few chemicals are effective in causing brain tumors experimentally after systemic administration of low doses; a notable exception is one group of N-nitroso compounds – the nitrosamides, in particular the nitrosoureas (4, 5). These cause brain tumors via various routes of administration and in a variety of species including monkeys (6). Tumor induction is highly effective when exposure is transplacental (7); relatively low levels of nitrosourea precursors (sodium nitrite and ethylurea) present in the food and drinking water of pregnant rats can cause a high incidence of tumor induction in offspring (8). This effect can be blocked if ascorbate, a nitrite scavenger, is also present (9, 10); and it is now well established that both vitamin C and vitamin E block the endogenous formation of N-nitroso compounds in animal stomachs and in human gastric juice in vitro (9, 10).

More is known about the sources of human exposure to nitrosamines, the other major subgroup of N-nitroso compounds, than about the sources of exposure to nitrosamides (11). For this reason, most epidemiological studies to date have investigated the relationship between brain tumors and sources of nitrosamine exposure such as tobacco smoke, which contains high levels of tobacco-specific nitrosamines, and foods and beverages that are known to contain low levels of nitrosodi-
methylamine and some other nitrosamines. Although nitrosamines have been tested extensively, they have not been shown to cause nervous system tumors in animals (5).

Most human exposure to nitrosamines seems likely to derive from compounds formed endogenously when precursors such as nitrite and an alkylamide (e.g., alkylurea, alkylcarbamate) are simultaneously present in the body, most importantly in the stomach. Unfortunately, little is known about the sources of alkylamides, although foods high in animal proteins and certain drugs are likely to be important. Some vegetables are high in nitrate, which in turn is a source of nitrite. The reduction of nitrate to nitrite occurs in the mouth, and saliva that contains low concentrations of nitrite is continually swallowed and enters the stomach, producing a highly diluted nitrite solution (11). Far higher concentrations of nitrite occur around bits of cured meats in the stomach after a meal that includes bacon or some other food cured with sodium nitrite. Such high concentrations of nitrite react most rapidly and are, therefore, most likely to lead to greater endogenous formation of nitrosamides and other N-nitroso compounds.

The present study, which covers 19 counties on the U.S. West Coast with established population-based cancer registries and is part of an international collaborative case-control study of CBTs3, is designed to focus on the hypothesis that N-nitroso exposures, in particular those occurring during gestation, are related to brain tumor development. Collaborators at nine centers in seven countries participated in this study. The present report includes the three U.S. centers and about half the total number of children with brain tumors.

Subjects and Methods
The U.S. West Coast CBT study was conducted to evaluate dietary and environmental risk factors among children less than 20 years old diagnosed with a brain tumor over a seven-and-a-half-year period. All eligible patients occurring in three regions of the U.S. were included: Los Angeles County; the five counties in the San Francisco-Oakland metropolitan area; and 13 counties in western Washington state, including the Seattle-Puget Sound metropolitan area. Control children were selected from the same geographic areas. To be eligible for inclusion in the study, the biological mother of the child had to be available for interview in English or Spanish, have a telephone, and provide informed consent. Recruiting methods were similar, and the in-person structured interview was the same for each study site.

Brain Tumor Patients. Children ages 0–19 years who were diagnosed with a primary tumor of the brain, cranial nerves, or cranial meninges (12) from January 1984 through December 1990 (Seattle and San Francisco) or June 1991 (Los Angeles) were identified from the cancer registry in each area; 813 cases were identified, and permission to contact the child's family was received from the physician of record for 790 cases (97%). Of these, 51 cases did not meet the eligibility criteria. Of the remaining 739 cases, the families of 106 (14%) children could not be located, 73 (10%) declined to participate, and 20 (3%) did not participate for other reasons. Thus, the mothers of 540 of the 739 (73%) case children who were determined to be eligible were interviewed for the study. Response rates were similar in all three geographic areas.

Controls. Controls were identified and recruited from the same three geographic areas using a two-step random digit dialing procedure (13). This procedure was designed to produce a comparison group that was similar in age and gender to the case group, at ratios of approximately two controls/case in Seattle and San Francisco and one control/case in Los Angeles. A list of area codes and telephone prefixes for each catchment area was compiled. Prefixes were randomly chosen from this list, and a randomly generated four-digit suffix was added to each. Interviewers called telephone numbers to determine if each was a residence, a business, or nonworking. Numbers were defined as "no answer" if at least nine attempts on various days and times did not provide an outcome. For each residence, the household was screened for eligible children, according to a defined protocol. If the household had more than one eligible child, a random number procedure was used to decide which child would be invited to participate. If the household had more than one residential telephone number, a random number procedure was used to select or reject the number called. Letters that described the study were sent to the mother of each eligible child selected to participate, and a second telephone contact was made to invite participation. For the three study sites combined, a screening interview to determine eligibility was completed for 6170 of 6990 (88.3%) residences. Mothers of 801 (67%) of the 1196 eligible children agreed to participate and were interviewed for the study; this was 75% of mothers who were invited to participate. Each participating control was assigned a reference date that corresponded to a diagnosis date for a similar case.

Exposure Information. Information on social and demographic factors and on potential brain tumor risk factors was collected during an in-person interview with the biological mother of each child. Throughout the interview, mothers were instructed to provide information only for exposures that preceded the date of diagnosis (cases) or the reference date (controls), hereafter called the reference date for both. Each mother was asked about her experiences during the pregnancy with the child and the child's experiences before the reference date. Questions covered sociodemographic factors; source of household drinking water; farm residence and contact with animals; smoking during pregnancy, and exposure to other people's tobacco smoke; family health history, including nervous system tumors, cancer, and radiation exposure; pregnancy and delivery history, including use of medications and vitamin supplements; reproductive history; child's feeding habits as an infant; history of head injury; and potential exposures to radiation and N-nitroso compounds. Maternal consumption during the past year and during the index pregnancy of 47 food items relevant to the N-nitroso hypothesis (i.e., major dietary sources of nitrate, nitrite, vitamin C, and vitamin E) was assessed with detailed dietary recall and abstract food models to gauge portion size (Table 1; Refs. 14–17). Only very limited data were collected on postnatal diet. The levels of nitrate in household drinking water were also assessed but were uniformly low and were unrelated to risk. A few questions were also asked about foods eaten in combination, including a question about how often vitamin supplements were taken with meals. Medication and vitamin use were assessed separately for five time periods: the month before pregnancy (to find out about the period very early

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3 The abbreviations used are: CBT, childhood brain tumor; OR, odds ratio; CI, confidence interval; SES, socioeconomic status.
in pregnancy before the woman knew she was pregnant); the first, second, and third trimesters; and while breast feeding.

**Statistical Analysis.** Unconditional logistic regression was used to derive the maximum likelihood estimates of ORs and corresponding 95% CIs to evaluate the strength of associations between brain tumor occurrence and maternal diet and vitamin use. Subjects with missing data for any variable were excluded from the analysis of that variable. Log transformations of the data provided a superior fit to the linear logistic model for analyses of continuous measures of exposure to vitamins; this was true to a lesser extent for cured meats. The original data were used to calculate the \( P \) values shown in tables unless otherwise indicated; log transform \( P \) values are reported in the text.

Nutrient levels in various foods were derived using published data and related software provided by Drs. Geoffrey Howe (Columbia University School of Public Health, New York, NY) and Gladys Block (University of California, Berkeley, CA). Analyses of the levels of nitrite in cured meats were done first, using values provided by Howe and again using values predicted by year for each type of cured meat from a comprehensive literature review.\(^5\) Similarly, comparison micronutrient analyses were done using the Howe and the Block values. Findings from both sets of alternative analyses were similar, and only analyses based on the Howe values are shown. We performed a market survey to determine the average levels of some micronutrients in various types of vitamin supplements (e.g., prenatal vitamins; regular, high potency, or stress formula multivitamins). Analyses of vitamin supplementation also used data on the frequency of taking vitamins with meals (never, sometimes, usually, or always) by assigning weights ranging from one to four.

Potential confounding was evaluated for age at reference date, year of birth, gender, race (Latino, other White, African American, and other), SES, and geographic area. Analyses were done using various measures of maternal, paternal, and parental (both parents considered simultaneously) SES (e.g., based on education alone, occupation alone, and education plus occupation). In situations in which one parent had multiple jobs or the SESs of the two parents were different, the child was assigned the higher SES. An SES index using information on both parents was derived using a scheme for weighting education and occupation that was similar to one described previously (18). Stratum-specific analyses were compared to evaluate potential effect modification for each of these variables and for trimester of intake and histology [astrocytomas and gliomas, morphology codes 9380–9384, 9400–9421, and 9424–9442; primitive neuroectodermal tumors, codes 9362, 9470–9473, and 9500 (formerly called medulloblastoma); and all other histologies were combined as a third category]. We also analyzed two time periods of the study separately: 1989 and later when case and control identification were concurrent; and 1988 and earlier when cases were identified before initiation of random digit dialing calls. Findings for the two periods or for children of different ages or in different geographic areas were similar unless stated otherwise. Modest differences in ORs were observed after adjusting for gender, year of birth, reference age, and geographic area. Thus, ORs adjusted for these variables are presented. No other confounding factors, including SES, were identified.

**Results**

Among cases, 55% were boys and 35% were less than 5 years old at diagnosis. A slightly higher proportion of control children were non-Latino white, and cases had lower SES than the controls (Table 2).

Risk was increased among children whose mothers ate any of four types of cured meats at least once a week, and risk increased with increasing consumption of bacon \((P = 0.0001, \) using log transformed data), hot dogs \((P = 0.002)\) and sausage

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The increase in risk related to vitamin supplementation was seen for all tumor types and geographic areas. Use of prenatal or other vitamin supplements was least common among Latinas, but controlling for ethnicity had little effect on risk estimates. Risk estimates were not affected by adjustment for reference year, age at diagnosis, SES, and maternal age at pregnancy. The effect of vitamin use was not seen for the month before pregnancy but was evident during all three trimesters, with the greatest reduction in risk evident during the second trimester (OR = 0.60 among mothers who took vitamins compared to those who did not take them during this period; CI = 0.45–0.80). Comparable ORs for the first trimester, third trimester, the month before pregnancy, and while breast feeding were 0.76, 0.69, 1.13, and 0.84, respectively; only CIs for each of the three trimesters excluded 1.0. Because the ability of vitamins C and E to block nitrosation is relevant to the nitroso hypothesis, the independent and joint effects of maternal vitamin and meat consumption were assessed in various ways. When the frequency of vitamin use (number of times taken/week averaged over the entire pregnancy) was weighted by the frequency of taking them with meals, the ORs were similar to those shown in Table 5, and the P value was 0.002. Table 7 shows that the increase in the risk of brain tumor among children whose mothers consumed more than 0.03 mg of nitrite from cured meats daily is substantially greater among those who did not take vitamins (OR = 2.2) than among those who did (OR = 1.3). No statistically significant interaction was seen between vitamin supplementation and either the mg of nitrite from cured meats (P for interaction = 0.23) or the frequency of cured meat consumption (P = 0.50).

### Discussion

This is the largest study to date to examine the role of maternal consumption of cured meats and vitamins in relation to CBTs. Our findings generally support the hypothesis that maternal intake of nitrite from cured meats increases brain tumor risk in their offspring, and the intake of vitamins that inhibit endogenous formation of carcinogenic nitroso compounds decreases...
194 subjects never used vitamins, least once a week; CI = strong association in Seattle (OR increase in risk related to hot dogs was mainly attributable to a primitive neuroectodermal tumors (23). In the present study, the dogs in the present study, in studies in Denver (21), and in a across the studies. For example, increased risk was seen for hot meats or decreases related to vitamin supplementation and/or U.S. also have tended to find increases in risk related to cured was solved to a question about "other drugs") and for dietary intake of foods rich in vitamin C (20). Studies in other areas of the U.S. also have tended to find increases in risk related to cured meats or decreases related to vitamin supplementation and/or vitamin rich foods, although the specific foods associated vary across the studies. For example, increased risk was seen for hot dogs in the present study, in studies in Denver (21), and in a country-wide study of astrocytic gliomas (22), but not one of primitive neuroectodermal tumors (23). In the present study, the increase in risk related to hot dogs was mainly attributable to a strong association in Seattle (OR = 2.8 for eating hot dogs at least once a week; CI = 1.6–4.9) where the level of hot dog intake was by far the highest; no increase in risk was seen in Los Angeles, where hot dogs are not commonly eaten by the largely Latino population. Of interest here are our findings that the average serving size (by weight) is greater for hot dogs than for any other cured meat, and that the amount of nitrite/g has declined for most cured meat products since 1970 but has increased dramatically for hot dogs, possibly because of concerns expressed in the media in the past couple of decades about potential health risks related to bacterial levels in hot dogs stored inappropriately for long periods (24).

Studies in other countries also have findings that support some, but not all, of our findings. A study in Canada found little increase in risk related to maternal intake of cured meats but did find fruit juices to be protective (25). In Australia, risk increased with increasing maternal intake of cured meats and decreased with increasing intake of vegetables (26).

Although, as noted above, our study has some variation in a few specific findings across subgroups of patients as defined, for example, by reference year or geographic area of residence, findings are generally consistent across all groups. We did not find that associations are limited to one half of the social class spectrum, to young children, or to only some tumor types, as found previously (23, 22). Data on postnatal diet were not available.

The limitations of this study must be considered in interpreting results. Although response rates in all groups were around 70% or higher, it is possible that respondents differed from nonrespondents in their distributions of variables studied. Control selection procedures may have introduced some undetectable bias. In Los Angeles County, where the population of children has become much more predominantly Latino over the study period, the differences in the study periods (1989 and later when identification of cases and controls occurred concurrently and 1984–1988 when it did not) led to quite distinct findings in relation to the configuration of electrical wiring outside the residence (27). This seems not to have led to major differences in an analysis of risk by period in relation to the use of electrical appliances or to most of the dietary and vitamin variables under consideration here, with the exception of maternal consumption of cured meats in Los Angeles, which shows no positive relation to risk among those with reference year in 1989 and later; this difference by period is not seen in the other two geographic areas. Risk estimates for this later time

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**Table 5.** Risk of childhood brain tumors by level of maternal consumption of cured meats during pregnancy, U.S. West Coast study, 1984–1991

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Average daily g cured meat</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;0.33</td>
<td>123 (24)</td>
<td>206 (26)</td>
<td>1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>0.33–1.2</td>
<td>121 (24)</td>
<td>201 (25)</td>
<td>1.1 (0.81–1.6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.25–16.56</td>
<td>122 (24)</td>
<td>209 (26)</td>
<td>1.1 (0.82–1.6)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;16.57</td>
<td>148 (29)</td>
<td>181 (23)</td>
<td>1.7 (1.2–2.3)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6.** Risk of childhood brain tumors by duration of maternal use of multivitamin supplements during pregnancy, U.S. West Coast study, 1984–1991

<table>
<thead>
<tr>
<th>Duration of daily use</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>OR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never took dailya</td>
<td>120 (23)</td>
<td>104 (13)</td>
<td>1.0</td>
<td>0.004</td>
</tr>
<tr>
<td>&lt;2 trimesters</td>
<td>57 (11)</td>
<td>67 (9)</td>
<td>0.68 (0.44, 1.07)</td>
<td></td>
</tr>
<tr>
<td>2 trimesters</td>
<td>155 (29)</td>
<td>240 (30)</td>
<td>0.55 (0.39, 0.77)</td>
<td></td>
</tr>
<tr>
<td>3 trimesters</td>
<td>201 (38)</td>
<td>377 (48)</td>
<td>0.54 (0.39, 0.75)</td>
<td></td>
</tr>
</tbody>
</table>

* 194 subjects never used vitamins, and 29 used them only occasionally or sporadically.

* p, using log transformed data.
Table 7 Risk of childhood brain tumors by average daily maternal consumption of cured meats in relation to use of prenatal vitamin supplements. U.S. West Coast study, 1984–1991

<table>
<thead>
<tr>
<th>Mg nitrite from cured meats</th>
<th>Took vitaminsa</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.3</td>
<td>Yes</td>
<td>195</td>
<td>354</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥0.3</td>
<td>Yes</td>
<td>219</td>
<td>338</td>
<td>1.3</td>
<td>(1.0, 1.7)</td>
</tr>
<tr>
<td>&lt;0.3</td>
<td>No</td>
<td>46</td>
<td>52</td>
<td>1.5</td>
<td>(0.93, 2.3)</td>
</tr>
<tr>
<td>≥0.3</td>
<td>No</td>
<td>47</td>
<td>40</td>
<td>2.2</td>
<td>(1.4, 3.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency of cured meat consumption&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤daily</td>
<td>383</td>
<td>639</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt;daily</td>
<td>50</td>
<td>50</td>
<td>1.9</td>
<td>(1.2, 2.8)</td>
</tr>
<tr>
<td>≤daily</td>
<td>89</td>
<td>82</td>
<td>1.6</td>
<td>(1.2, 2.3)</td>
</tr>
<tr>
<td>&gt;daily</td>
<td>9</td>
<td>9</td>
<td>2.1</td>
<td>(0.79, 5.4)</td>
</tr>
</tbody>
</table>

* OR (95% CI) for vitamin use adjusted for > daily intake of cured meat = 0.64 (0.47, 0.89; P = 0.007).
* P for independent effect of variable (cured meat; vitamins) after other variable has been considered.
* OR (95% CI) for cured meat > daily adjusted for took vitamins = 1.7 (1.2, 2.6; P = 0.005).

period are imprecise because of the relatively small numbers, and random variation may be an explanation.

Recall of diet during pregnancies that occurred many years ago may be poor, although dietary recall for past pregnancies has been shown to be quite good, and recall of vitamin use during pregnancy in relation to adverse outcome has been shown to be unbiased (28). Such unbiased misclassification would tend to make true differences between cases and controls more difficult to identify. The potential for biased recall, which is a serious concern, could have occurred if the mothers of children with cancer more fully reported their consumption of foods such as cured meats that were viewed as unhealthy. The fact that no increased risk is seen for the other foods on the list that also are likely to have been considered unhealthy (e.g., raw or rare meat and alcoholic beverages) argues against such bias as an explanation for the associations seen with cured meats.

Although we hypothesized that most exposure of mothers to nitrosamides resulted from endogenous formation and that in this regard cured meats would be the most important source of dietary nitrite, we are unable to evaluate sources of exposure to alkylamides because they have not been defined as yet. We further hypothesized that the effect of cured meats would be modified by intake of vitamins C and E, which block endogenous formation of nitrosocompounds. The West Coast study supports our expectation both of an increase in risk related to cured meats and a decrease related to these (and other) vitamins. However, we do not know whether the protection conferred by vitamins relates to the inhibition of nitrosation or to some other protective mechanism such as antioxidant effects (29). Because correlations between consumption of these vitamins and other micronutrients are so high, the present study is also unable to determine whether the protection is specifically from vitamins C and E (as predicted by the nitroso hypothesis) or from other micronutrients such as vitamin A or folate, which in our data appear similarly protective. Prenatal and other multivitamin compounds contain all of the micronutrients shown in Table 6 in addition to others, and several of the foods on our short list also contain relatively high levels of more than one micronutrient. However, our short food list was designed only to assess intake of vitamins C and E, and it may be inadequate or even misleading when used to investigate other micronutrients. Studies with more complete dietary survey information on maternal diet during pregnancy may help to sort out some of these issues. It is hoped that when such data are available, laboratory work will have identified important dietary sources of alkylureas and other alkylamides. Laboratory work is also needed to investigate the reactivity of nitrite in high concentration (such as around bits of cured meats in the stomach after ingestion) compared to nitrite in dilute solution and to confirm that simultaneous ingestion of alkylamides and cured meats leads to the endogenous formation of nitrosamides.

Acknowledgments

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