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Processed meats and risk of childhood leukemia (California, USA)

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The relation between the intake of certain food items thought to be precursors or inhibitors of N-nitroso compounds (NOC) and risk of leukemia was investigated in a case-control study among children from birth to age 10 years in Los Angeles County, California (United States). Cases were ascertained through a population-based tumor registry from 1980 to 1987. Controls were drawn from friends and by random-digit dialing. Interviews were obtained from 232 cases and 232 controls. Food items of principal interest were: breakfast meats (bacon, sausage, ham); luncheon meats (salami, pastrami, lunch meat, corned beef, bologna); hot dogs; oranges and orange juice; and grapefruit and grapefruit juice. We also asked about intake of apples and apple juice, regular and charcoal broiled meats, milk, coffee, and coke or cola drinks. Usual consumption frequencies were determined for both parents and the child. When the risks were adjusted for each other and other risk factors, the only persistent significant associations were for children's intake of hot dogs (odds ratio [OR] = 9.5, 95 percent confidence interval [CI] = 1.6-57.6 for 12 or more hot dogs per month, trend $P = 0.01$), and fathers' intake of hot dogs (OR = 11.0, CI = 1.2-98.7 for highest intake category, trend $P = 0.01$). There was no evidence that fruit intake provided protection. While these results are compatible with the experimental animal literature and the hypothesis that human NOC intake is associated with leukemia risk, given potential biases in the data, further study of this hypothesis with more focused and comprehensive epidemiologic studies is warranted. *Cancer Causes and Control* 1994, 5, 195 - 202

Key words: Childhood leukemia, hot dogs, processed meats, nitrites, N-nitroso compounds, United States.

Introduction

This case-control study of childhood leukemia was conducted in Los Angeles County, California (United States), to explore a variety of factors suspected to be related etiologically to the development of this disease, including environmental chemicals, electric and magnetic fields, past medical history, parental smoking and drug use, and dietary intake of certain food items thought to contain carcinogens or protective agents. This article focuses on these dietary factors. Most items on the short food-list used for this study were included

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because of their relevance to the formation of N-nitroso compounds (NOC). Previous publications have considered some of the other hypotheses.[1,2] Two other articles on this subject are published in this issue.[3,4]

Materials and methods

Subjects

All newly diagnosed cases of leukemia occurring between 1980 and 1987 in children from birth to age 10 years and resident in Los Angeles County were eligible. Cases were identified by the Los Angeles County Cancer Surveillance Program.[5,6] We asked permission of the patient's physician to contact the parents for interview. With the physician's consent, we attempted to locate and contact the patient's parents to gain permission for interview. We interviewed 232 case-control pairs. The original report by Lowengart[1] included data on 123 cases diagnosed from 1980 to 1984 and their matched controls. An additional 27 case-control pairs identified were excluded from the original report because of missing information. The first 65 controls were drawn from friends of cases; all subsequent controls were selected by random-digit dialing. For the supplementary study, we attempted to recontact all 150 pairs identified from the original study and completed interviews for 139 cases and 131 controls. Additionally, we replaced eight controls (including three friend-controls) whom we could not reach with new controls contacted through random-digit dialing. We also interviewed 93 cases diagnosed from 1985 to 1987 and 93 controls selected by random-digit dialing.

In the random-digit dialing procedure, the area code and the first five digits of the case's telephone number were used, followed by a random choice of the last two digits. We attempted to match individually on gender, ethnicity (Black, White, Hispanic, and Asian), and age. The age-matching alogorithm varied with the case's age: within one year of the case's age at the time of diagnosis, for cases under age two years; within two years for cases aged three to five years; and within three years for cases aged six years or older. When the matching rules were not met after 300 calls, we relaxed matching criteria first on ethnicity, then on gender, and finally on age. Cases and controls were comparable with regard to matching factors.[2] For the original study,[1] our records do not allow computation of the number of contacts per eligible control identified. In the supplementary study,[2] 4,424 telephone numbers were called and 800 yielded no answer after nine attempts. Among 3,624 contacts made: 3,303 subjects were ineligible; eligibility could not be determined for 208; 113 were eligible and 102 agreed to participate, of whom, one was not used. Among 331 cases identified as eligible, interviews were completed for 252 (20 for whom no control could be found). The difference was accounted for by 22 physician refusals, 24 parent refusals, and 33 untraceable cases.

Questionnaires

We attempted to interview both parents. When the father could not be interviewed (19 percent of case fathers and 29 percent of control fathers), we asked the mother to provide information about him. Interviews were conducted by telephone in either English or Spanish. The interview included a complete history of the children's residences, demographics, basic medical history of the child and parents, use of medications, and occupational history for both parents. We also gathered information on the location and temporal pattern of the children's activity, history of appliance use, and exposure to environmental chemicals, recreational drugs, and incense.

Twelve questions were asked about the *usual* dietary intake and frequency of certain food items, some of which contain precursors (*e.g.*, nitrite) or inhibitors (*e.g.*, vitamin C) of NOC. In addition, neutral items such as coke and cola drinks were added to be able to assess possible response bias. It is assumed that most exposure of our study population to NOC is from those formed in the body.[7] Questions on usual frequency of consumption were included for each of the following food items: bacon, sausage and ham combined (referred to as breakfast meats for brevity); hot dogs; hamburgers; bologna, pastrami, corned beef, salami, or lunch meats combined (referred to as lunch meats for brevity); charcoal broiled meats; oranges or orange juice; grapefruit or grapefruit juice; apples or apple juice; coffee; coke or cola drinks; pasteurized milk; and raw milk. The mother was asked to provide the information for herself and then to estimate how often the child ate these items up to the reference period.[2] The father was asked to provide his dietary information.

Statistical analysis

The 232 matched pairs with residential histories serve as the basic study population. The numbers available for analysis of particular exposure variables vary slightly because of missing data on some of the subjects. If data on a factor were not available on both members of a matched pair, that pair was eliminated from the analysis of that factor.

To divide the frequency of food use into categories

for matched logistic regression, we first examined the distribution of responses without knowledge of case or control status. The cut-points were made based partly on sample size and partly on the distribution of responses. Depending on response frequencies, data were divided into two, three, or four levels for analysis.

Various potential occupational and environmental confounders were examined univariately, treating each as dichotomous with standard matched-pair methods. We then included as covariates in a multiple logistic regression all those potential confounders adjusted for in our earlier publication,[2] plus wiring configuration. The former were selected by a backwards elimination procedure, retaining variables that had one-sided *P*-value of less than 0.10 in the final model, irrespective of their association with the exposure variables. To this set, we added the additional dietary variables that met the same criterion, as indicated by footnotes in Table 4.

Results

Table 1 contains data on children's leukemia risks associated with the intake of various meats by the mother, the father, and the child. Parental consumption of 'ham, bacon and/or sausage' conveyed no apparent risk to the child. However, there was a

Table 1. Odds ratios for childhood leukemia according to maternal, paternal, and children's ingestion of various meats

	Servings per month				CI[a] for highest category	Trend (*P*)
	None (0)	Low (1-3.9)	Medium (4-11.9)	High (12+)		
Ham, bacon, and sausage						
Mother	1.0	0.7	1.0	1.0	(0.5-2.0)	0.8
Case/Control	75/67	65/84	64/55	25/23		
Father	1.0	0.5	0.9	1.0	(0.5-1.9)	0.3
Case/Control	51/45	50/74	81/72	41/32		
Child	1.0	1.0	1.2	2.7	(1.4-5.3)	0.02
Case/Control	83/94	47/54	59/62	40/19		
Hot dogs						
Mother	1.0	0.9	1.8	2.4	(0.7-8.1)	0.1
Case/Control	106/110	79/92	30/18	10/5		
Father	1.0	1.3	1.5	5.1	(1.4-18.4)	0.008
Case/Control	69/86	99/98	41/35	14/4		
Child	1.0	1.4	1.7	5.8	(2.1-16.2)	0.001
Case/Control	69/90	69/77	65/54	24/6		
Bologna, pastrami, salami, corned beef, and lunch meat						
Mother	1.0	1.0	1.0	1.3	(0.8-2.4)	0.5
Case/Control	103/107	49/48	41/46	37/29		
Father	1.0	1.5	0.8	1.7	(1.0-2.9)	0.2
Case/Control	60/70	49/40	51/69	66/48		
Child	1.0	1.0	1.2	1.6	(1.0-2.8)	0.08
Case/Control	94/105	29/34	54/53	54/39		
Hamburgers						
Mother	1.0	1.2	0.9	1.2	(0.5-2.5)	0.9
Case/Control	53/56	82/71	73/83	23/21		
Father	1.0	1.2	0.9	0.9	(0.5-1.8)	0.6
Case/Control	42/42	61/51	79/89	42/42		
Child	1.0	1.5	1.5	2.3	(1.0-5.2)	0.4
Case/Control	75/92	54/50	80/76	21/12		
Charbroiled meats						
Mother	1.0	1.2	1.1	0.9	(0.5-1.8)	1.0
Case/Control	66/72	91/83	44/42	25/29		
Father	1.0	1.1	1.0	0.7	(0.4-1.2)	0.2
Case/Control	52/52	94/80	37/35	37/53		
Child	1.0	1.4	1.6	1.0	(0.4-2.1)	0.4
Case/Control	101/115	77/67	37/29	16/20		

[a] CI = 95% confidence interval.

Table 2. Odds ratios for childhood leukemia according to maternal, paternal, and children's ingestion of various fruits and fruit drinks, coke and cola drinks

	Servings per month				CI[a] for highest category	Trend (*P*)
	None (0)	Low (1-7.9)	Medium (8-29.9)	High (30+)		
Oranges or orange juice						
Mother	1.0	0.9	0.6	0.8	(0.5-1.4)	0.3
Case/Control	43/34	53/45	51/71	82/79		
Father	1.0	0.9	1.2	1.1	(0.6-2.1)	0.4
Case/Control	35/36	58/69	73/66	57/52		
Child	1.0	1.4	1.8	1.1	(0.6-1.9)	0.7
Case/Control	46/57	45/43	76/56	63/74		
Grapefruit or grapefruit juice						
Mother	1.0	1.0	0.5	1.1	(0.5-2.7)	0.3
Case/Control	166/156	36/35	14/27	13/11		
Father	1.0	0.7	0.8	—	(0.5-1.5)	0.3
Case/Control	157/143	38/49	31/34			
Child	1.0	0.8	1.0	—	(0.5-2.1)	0.7
Case/Control	203/199	16/20	13/13			
Apple juice						
Mother	1.0	0.9	1.0	0.9	(0.5-1.4)	0.6
Case/Control	56/51	62/63	30/28	82/88		
Father	1.0	1.6	1.0	1.2	(0.7-2.1)	0.8
Case/Control	56/65	55/40	57/65	55/53		
Child	1.0	2.6	1.2	1.6	(0.9-2.9)	0.5
Case/Control	29/42	38/23	20/28	144/138		
Coke or cola drinks						
Mother	1.0	0.8	1.0	1.0	(0.6-1.6)	0.9
Case/Control	92/91	20/25	43/41	73/71		
Father	1.0	1.3	0.8	1.2	(0.7-1.9)	0.9
Case/Control	53/55	37/30	50/62	89/82		
Child	1.0	2.2	1.7	2.6	(1.5-4.5)	0.0008
Case/Control	86/119	30/23	41/37	74/52		

[a] CI = 95% confidence interval.

statistically significant trend across categories of children's intake and the risk in the highest consumption category was significantly elevated. We observed a different pattern for hot dogs. There was a suggestive but not statistically significant increase for maternal consumption while both paternal and children's intake were associated with significant trends and elevated risks in the highest category. No association with 'lunch meats' or charcoal broiled meats was observed. For hamburgers, children's consumption showed a rising trend and an elevated risk in the highest exposure category.

There was no evidence that fruit or fruit drinks conveyed protection from risk (Table 2). Children's con-

Table 3. Correlation (Spearman) between intake of certain food items

	1	2	3	4	5	6	7
Children's consumption							
Hot dogs	1.0	0.49	0.46	0.52	0.38	0.41	0.17
Bacon, ham, sausage		1.0	0.40	0.49	0.39	0.47	0.15
Lunch meats[a]			1.0	0.50	0.35	0.30	0.16
Hamburgers				1.0	0.33	0.38	0.21
Charcoal broiled					1.0	0.35	0.09
Coke or cola drink						1.0	0.12
Fathers' consumption of hot dogs							1.0

[a] Includes salami, pastrami, lunch meat, corned beef, bologna.

sumption of 'coke or cola drinks' was associated positively with risk, although risk estimates did not increase monotonically. Consumption of 'coke or cola drinks' by parents did not convey risks to the child (Table 2). There was no apparent risk associated with coffee or milk consumption (data not shown).

To evaluate possible correlation between father's and children's consumption of the food items under study, we computed Spearman correlation coefficients for the children's food items in Table 1 and the children's consumption of coke or cola drinks (Table 3). The children's consumption of all meats was correlated with intake of 'coke or cola drinks.' Fathers' consumption of hot dogs was correlated less well with children's consumption of hot dogs (Spearman correlation was 0.17).

We then conducted multiple logistic-regression analyses of these food items and added factors previously found in this study to be risk factors.[2] These factors were self-reported use of indoor pesticides, children's use of hair dryers and black and white televisions, incense use, fathers' occupational exposure to spray paints during pregnancy and other chemical exposures post pregnancy, and wiring configuration.[2] On the basis of the results just presented, we initially included the following factors in our analyses: paternal consumption of hot dogs; children's consumption of hot dogs; children's consumption of ham/bacon/sausage; children's consumption of hamburgers; children's consumption of lunch meats; and children's consumption of 'coke or cola drinks'. One other factor, breast feeding, found to have borderline risk was also added to the model.

In Table 4, we present our final models showing the effect of adjustment for these other significant factors. The risk associated with children's consumption of hot dogs persisted after adjustment for other risk factors including fathers' consumption of hot dogs. On the other hand, the risk associated with children's consumption of 'coke or cola drinks' became nonsignificant after adjustment for the other risk factors. The two factors accounting for the decreased risk associated with consumption of 'coke or cola drinks' were fathers' and children's consumption of hot dogs. The risk seen for children's consumption of breakfast meat largely disappeared after adjustment for the other risk factors. The same was true for consumption of both lunch meat and hamburger.

Since the risks associated with consumption of hot dogs persisted for both father and child after adjustment for each other and the other risk factors, we examined the question of what the risk would be if both the child and the father were heavy consumers of hot dogs. We first cross-tabulated by father's and child's exposure and looked at the cell of highest consumption for both. There were only five subjects in this cell, so we included the next highest cell for each. We then compared the three cells (high-high, high-medium, or medium-high) with the cell in which neither the child nor the father consumed hot dogs. The risk, adjusted for all other significant factors, was 19.8 (CI = 3.4-115.5).

While the dose-response trends for adjusted consumption of hot dogs for both fathers and children were highly significant (Table 4), the risks did not become large until the high category. For children, the average number of hot dogs consumed was 1.3 per month for low, 5.8 for medium, and 19.7 for high. For fathers, they were 1.2 per month for low, 5.1 for medium, and 23.0 for high.

We examined whether the risk associated with the fathers' or children's consumption was modified by age. There was no apparent age relationship with either (data not shown).

We also looked at whether the association between intake of hot dogs and leukemia risk varied by the gender of the case. For both fathers' and children's consumption of hot dogs, the risks were higher for males even though the categories of consumption frequency were the same for both genders. The test for heterogeneity, however, was not statistically significant. If we examine the risk in males associated with both children's and fathers' consumption of hot dogs being in high-high, medium-high, or high-medium categories, there were 12 cases and no controls ($P = 0.003$, data not shown).

While most of the cases were acute lymphocytic leukemia (ALL), we did look at risk by whether cases were ALL or acute non-lymphocytic leukemia (ANLL) by fathers' and children's consumption of hot dogs. There were no apparent differences by leukemia type.

Discussion

Our results provide evidence for an association between consumption of hot dogs and risk of childhood leukemia. Adjustments for all factors thought to be potential confounders did not affect these associations. Independent risks were associated with both children's and fathers' consumption. The former risk may be a direct result of ingestion of NOC precursors and other substances which are transformed eventually into leukemogens. The risk associated with father's consumption requires other mechanisms that would affect germinal tissues that are conveyed subsequently to the child. Experimental work has shown a high occurrence

Table 4. Multiply-adjusted odds ratios (OR) between childhood leukemia risk and intake of various food items

Trend	Intake				*P*
	None	Low	Medium	High	
Children's hot dog consumption					
Adjusted OR[a]	1.0	0.6	1.3	9.5	0.01
(CI)[b]	—	(0.3-1.5)	(0.6-3.0)	(1.6-57.6)	
Case/Control	43/47[c]	38/55	44/34	14/3	
Fathers' hot dog consumption					
Adjusted OR[d]	1.0	0.9	3.1	11.0	0.01
(CI)[b]	—	(0.5-1.7)	(1.2-8.0)	(1.2-98.7)	
Case/Control	45/57	57/61	30/18	7/3	
Children's coke or cola consumption					
Adjusted OR[e]	1.0	1.5	0.5	1.3	0.8
(CI)[b]	—	(0.5-4.1)	(0.2-1.1)	(0.5-3.4)	
Case/Control	53/62	19/15	23/28	44/34	
Children's ham/bacon/sausage consumption					
Adjusted OR[e]	1.0	0.8	0.7	1.3	1.0
(CI)[b]	—	(0.4-1.7)	(0.3-1.7)	(0.4-4.5)	
Case/Control	47/50	33/33	33/43	24/11	
Children's lunch meat consumption					
Adjusted OR[e]	1.0	0.6	1.0	1.4	0.4
(CI)[b]	—	(0.3-1.5)	(0.4-2.5)	(0.6-3.4)	
Case/Control	51/59	17/28	34/28	37/24	
Children's hamburger consumption					
Adjusted OR[e]	1.0	0.7	0.6	1.0	0.5
(CI)[b]	—	(0.3-1.7)	(0.2-1.4)	(0.3-3.8)	
Case/Control	46/49	33/33	49/48	10/8	

[a] Adjusted for self-reported use of indoor pesticides, children's hair dryers, fathers' occupational spray paint, fathers' other occupational chemicals, fathers' hot dog consumption, wiring configurations, and nursing.

[b] CI = 95% confidence interval.

[c] Numbers are smaller than in Table 1 due to missing data on individual confounding factors.

[d] Adjusted for self-reported use of indoor pesticides, children's hair dryers, father's occupational spray paint, father's other occupational chemicals and child's hot dog consumption, wiring configurations, and nursing.

[e] Adjusted for self-reported use of indoor pesticides, children's hair dryers, fathers' occupational exposure to spray paint, other occupational chemical exposure, fathers' and children's hot dog consumption, wiring configurations, and nursing.

of a gene mutation that predisposes progeny to tumor development at an early age in male mice treated with N-nitrosoethylurea before mating.[8] Risks associated with paternal occupational exposures seen in this[1] and other studies may involve similar mechanisms. We had postulated, before looking at the data, that fathers' consumption of hot dogs might produce an increased risk in younger children and that the child's consumption of hot dogs might be associated preferentially with risk in older children. The data did not clearly support either.

Cured meats have been of interest in studies of childhood brain tumors and other cancers thought possibly to relate to exposure to NOC.[9-11] The strongest experimental evidence that perinatal exposure to NOC causes leukemia and lymphoma implicates the nitrosoureas. N-nitrosomethylurea (MNU), -ethylurea (ENU) and -butylurea (BNU) are moderately to highly effective perinatal leukemogens in mice and rats, and neonatal exposure is more effective than transplacental exposure.[12,13] Nitrosoureas are a subgroup of nitrosamides (the other major group of nitroso compounds besides nitrosamines) that are not often tested in consumer products and environments because they are difficult to measure,[7] but it is likely that most human exposure to these compounds occurs from their formation in the body during the simultaneous presence of precursors such as nitrite and an alkylurea.

Recent studies also show that MNU is produced during nitrosation of various foods with the highest levels, by far, occurring in processed fish and meat.[14]

In addition, certain nitrosamines have been shown to cause hematopoietic cancers after perinatal exposure to rats or mice including N^6 (methylnitroso) adenosine (MNAR) which has been identified tentatively in a mixture of foods including cured meats,[15] and dinitrosopiperazine which is formed by nitrosation of a fungicide.[16]

It is also possible that cured and/or charbroiled meats contain other compounds that may be leukemogenic. Urethane is the most effective newborn leukemogen in mice.[17] Also, in newborn mice, lymphatic tissue is one of the biological systems that is most sensitive to the effects of carcinogenic chemicals.[17] Urethane is present in human foods as a fermentation product,[18] although it is not known whether it might be present in hot dogs or other cured meats that are less than fresh. Polycyclic aromatic hydrocarbons (PAH) are present in meats after charcoal broiling or other open-fire cooking,[19] and PAHs, especially dimethylbenz[a] anthracene (DMBA) cause leukemia after transplacental or neonatal exposure.[17]

While the biological plausibility of our findings exists and the possible toxicologic mechanisms should be explored, we believe it is important to pursue this finding with other human studies. It is possible that the association we report is spurious. All case-control studies are beset by potential biases.

Potential bias. A large number of controls were selected by random-digit dialing. We cannot prove that this system generates a control group that is representative of the same population from which the cases arose. To achieve the results presented here, we could be undersampling the heavy hot-dog eaters in our control group, producing a false association. If our control group is not representative, we would expect to find differences in measures of socioeconomic status (SES). Our analysis shows very similar socioeconomic indices in the cases and controls as measured by SES, mother's or father's education and occupational factors (blue *cf* white collar). Adjustment for SES did not affect the relationship between consumption of hot dogs and leukemia risk.

Recall bias is another possible explanation of our findings. Parents of leukemia cases may try harder to remember past exposures that could explain their child's illness than parents of controls. It seems unlikely that recall bias explains our findings unless one postulates that parents of cases know or think that hot dogs are more harmful than other meats. Alternatively, our findings could result if parents are better able to recall the use of hot dogs than other foods. However, we have no data to address this possibility.

Confounding by intake of foods associated with consumption of hot dogs should be considered. For example, hot dogs are eaten frequently with mustard and/or catsup. We know of no reason to suspect these condiments. In our analysis, we adjusted for a large number of factors thought to be associated with leukemia risk. Since there is relatively little known about the etiology of childhood leukemia, confounding by a factor not yet known to be a disease risk is possible. If such a factor exists, the risk associated with it would need to be very large and tightly associated with consumption of hot dogs to have produced spuriously the results presented here. It is interesting to note that when we analyzed the risks associated with wiring configuration,[2] we did not know about the paternal and children's risk associated with hot dogs. Adjustment of the wiring-configuration risk for these two factors had little effect on the risk (matched OR before adjustment was 2.3, and after was 2.0 in the high wiring-configuration category).

Since the hypothesis related to NOC was one of many we were attempting to assess and the questionnaire was already very long, the questions we asked were brief and not comprehensive. We believe our findings justify further testing of this hypothesis with other study populations and a more complete examination of food items of potential importance. This should include information on temporal patterns, cooking methods, brand names, associated foods, portion sizes, and timing of intake of various foods and vitamin supplements.

The hypothesis that NOC exposures relate to the development of leukemia in children would expect a protective effect for foods such as citrus which are high in vitamin C and are important inhibitors of endogenous nitrosation if present in body fluids (such as gastric contents) when N-nitroso precursors are present. We did not see such a protective effect, but we would not expect one if, for example, the child drank orange juice at breakfast but ate hot dogs later in the day.

Most importantly, our findings suggest the potential importance of diet in the etiology of leukemia, a disease whose etiology is not well understood. Studies of diet in relation to leukemia in both children and adults are indicated.

The findings, if correct, suggest that reduced consumption of hot dogs could reduce leukemia risks, especially in those consuming the most. While there is clearly a dose-response association, the risks did not become large until consumption exceeded 12 hot dogs per month for both children and fathers. Until further studies are completed and this issue becomes clearer, it

may be prudent for parents to consider reducing consumption of hot dogs for themselves and their children where consumption frequencies are high.

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