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Food Consumption by Children and the Risk of Childhood Acute Leukemia

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The possible relation between child's early diet and risk of childhood leukemia has remained largely unexplored. The authors' objective was to determine what particular foods consumed early in life (first 2 years) are associated with risk of childhood leukemia in a 1995–2002 case-control study of a diverse California population. Dietary data were obtained from a questionnaire administered to the child's caregiver. Conditional logistic regression was used to analyze 328 case-control sets matched on age, sex, Hispanic status, and maternal race. Regular consumption of oranges/bananas (odds ratio = 0.49, 95% confidence interval: 0.26, 0.94) and orange juice (odds ratio = 0.54, 95% confidence interval: 0.31, 0.94) during the first 2 years of life was associated with a reduction in risk of childhood leukemia diagnosed between the ages of 2 and 14 years. Restricting the analysis to leukemia diagnosed between the ages of 2 and 5 years reflected a similar pattern of reduced risk. No association between eating hot dogs/lunch meats and risk of leukemia was found. These results suggest that fruits or fruit juices that contain vitamin C and/or potassium may reduce the risk of childhood leukemia, especially if they are consumed on a regular basis during the first 2 years of life.

ascorbic acid; case-control studies; child; diet; epidemiologic methods; leukemia; nutrition

Abbreviations: CI, confidence interval; NCCLS, Northern California Childhood Leukemia Study; OR, odds ratio.

Nutrition has been implicated in possibly reducing the risk of adult solid tumors such as colorectal, prostate, lung, and breast (1, 2), while its association with a reduction in risk of adult leukemia has only been recently shown (3). Despite these findings, research into the effects of a child's diet on the risk of childhood leukemia, the leading cause of cancer morbidity under the age of 15 years (4), has been rare. Little emphasis has been placed on diverse aspects of the diet and the timing of exposure.

The primary focus of study related to child's diet and risk of childhood cancer has been the *N*-nitroso hypothesis and childhood brain tumors (5, 6). Maternal consumption during pregnancy or child consumption early in life of cured meats, which contain *N*-nitroso precursors, could lead to the formation of carcinogenic *N*-nitroso compounds in the acidic stomach (7). Subsequently, these compounds could be transported to brain tissue in the developing embryo or the young child, ultimately increasing the risk of childhood brain tumors (8). Animal experiments have shown that pregnant rats fed *N*-nitroso precursors, specifically nitrites and amines/amides, are at an increased risk of producing offspring with brain tumors (9). This effect is attenuated when vitamins C and E, which block the nitrosation reaction necessary to create carcinogens, are fed to rats simultaneously with *N*-nitroso precursors (10). This hypothesis can be extended to other childhood cancers such as leukemia and lymphoma (8).

In the current epidemiologic literature, with the exception of the study by Ross et al. (11) on infant leukemia, only two case-control studies (12, 13) that address the possible relation of child's diet and the risk of childhood leukemia have been conducted. Both investigations concentrated on the *N*-nitroso hypothesis by using data describing maternal, child, and/or paternal consumption of cured meats.

To expand on the published research addressing child's diet and the risk of childhood leukemia, we have undertaken an analysis to determine which dietary constituents during a child's early diet (first 2 years of life) are associated with the risk of childhood leukemia. Emphasis was placed on not only a wider spectrum of foods and frequency of exposure but also

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the timing of exposure early in life. Furthermore, the objective was to evaluate the *N*-nitroso hypothesis in a well-designed, case-control study of a diverse California population.

MATERIALS AND METHODS

Study population

The Northern California Childhood Leukemia Study (NCCLS) is a matched case-control study that began in 1995. This analysis consists of data collected from two phases of the study: phase 1 from August 19, 1995, to November 30, 1999, and phase 2 from December 1, 1999, to November 30, 2002. Incident childhood leukemia cases were identified on the basis of *International Classification of Diseases for Oncology* criteria (14), using a rapid case ascertainment procedure from seven (phase 1) and expanded to nine (phase 2) pediatric hospitals in the northern and central California study region. During phase 1, the study area encompassed 17 counties in the greater San Francisco-Oakland Bay area, while during phase 2, the area expanded to 35 counties including the Central Valley of California. Comparison with the statewide California Cancer Registry for 2000 showed that 95 percent and 76 percent of eligible cases among residents in the five-county San Francisco-Oakland Metropolitan Statistical Area and in the other 30 counties of the study area, respectively, were identified by the NCCLS protocol. The evaluation of case ascertainment for all 35 counties is currently underway. Cases were eligible if they were under 15 years of age, had no previous history of any malignancy, lived within the study region, and had parents who spoke either English or Spanish. The study was approved by the University of California Committee for the Protection of Human Subjects, the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the institutional review boards of the participating hospitals. Written informed consent was obtained from the parents of all participating subjects.

After each case was identified, a control subject was selected from birth certificates through the California Office of Vital Records. Birth certificates were matched 1:1 (phase 1) or 1:2 (phase 2) to the case on date of birth, sex, Hispanic status (a child is considered Hispanic if either parent is Hispanic), maternal race, and maternal county of residence at birth (only phase 1). Matching on maternal county of residence at birth was not pursued in phase 2 because of concerns regarding overmatching on potential environmental exposures related to leukemia risk. If the case child was not born in California (7 percent of cases), controls were selected from the case county of residence at diagnosis. Out-of-state cases were comparable to cases born in California on age, sex, Hispanic status, and maternal race. For each case, four or more potential controls were identified from the California birth registry and then randomized for selection. If the first-choice control could not be located, was ineligible, or refused to participate, the next randomly ordered control was contacted until an eligible control agreed to participate.

As of December 1, 2002, 283 case-control pairs matched 1:1 and 100 case-control triplets matched 1:2 of leukemia were obtained. Since the critical period of exposure in this dietary analysis was the first 2 years of life, and since different risk factors might exist for infants who develop leukemia (15, 16), cases and their respective controls under 2 years of age were excluded. By this criterion, 42 pairs and 13 triplets of childhood leukemia diagnosed at less than 2 years of age were excluded, which left 241 pairs and 87 triplets for the analysis. Of these, 204 pairs and 81 triplets were of the acute lymphoblastic leukemia subtype. The overall case participation rate was 86 percent (83 percent in phase 1 and 89 percent in phase 2). The overall control participation rate was 56 percent (49 percent in phase 1 and 64 percent in phase 2), which was the number of controls enrolled divided by the number of birth controls sought, excluding ineligibles (figure 1). The reasons of nonparticipation for the eligible and presumed eligible controls included refusal (26 percent) and could not be found (18 percent). This participation rate is better than the 49 percent rate reported in another study of childhood leukemia in New York State that used birth certificate controls (17). Further details of NCCLS control recruitment can be found elsewhere (18).

Data collection

During phase 1, child's dietary data were collected by a mailed caregiver questionnaire that was completed by the biologic mother before conducting the in-home interview. During phase 2, child's dietary data were gathered by a caregiver questionnaire that was completed by the biologic mother following the completion of the in-home interview. Most often, the biologic mother provided the information on the caregiver questionnaire and in-home interview (95 percent). The wording of the dietary questions did not differ between the two phases. The questionnaire asked about the child's weaning history and the frequency of consumption of nine foods/food groups during the child's first and second years of life: hot dogs/lunch meats, beef/hamburger, vegetables, oranges/bananas, apples/grapes, orange juice, fruit juice, milk, and soda. The frequency categories for the responses were rarely or never, 1–3 days/week, 4–6 days/week, almost every day, twice a day, and three or more times a day. In addition, whether or not the child consumed vitamins during the first 2 years of life was assessed. The dietary questionnaire was designed to be completed in 15 minutes.

Data management

Frequency categories on the questionnaire were collapsed into simpler categories for both the first and second years of life to eliminate small numbers of observations. To summarize food consumption over the first 2 years of life, we created new categories of "rare/no consumption," "occasional consumption," and "regular consumption" based on the original categories (table 1). All the foods/food groups had sufficient numbers of cases and controls in each category (table 2).

Statistical analysis

Selected characteristics of cases and controls were compared with the Pearson chi-squared test. Correlations

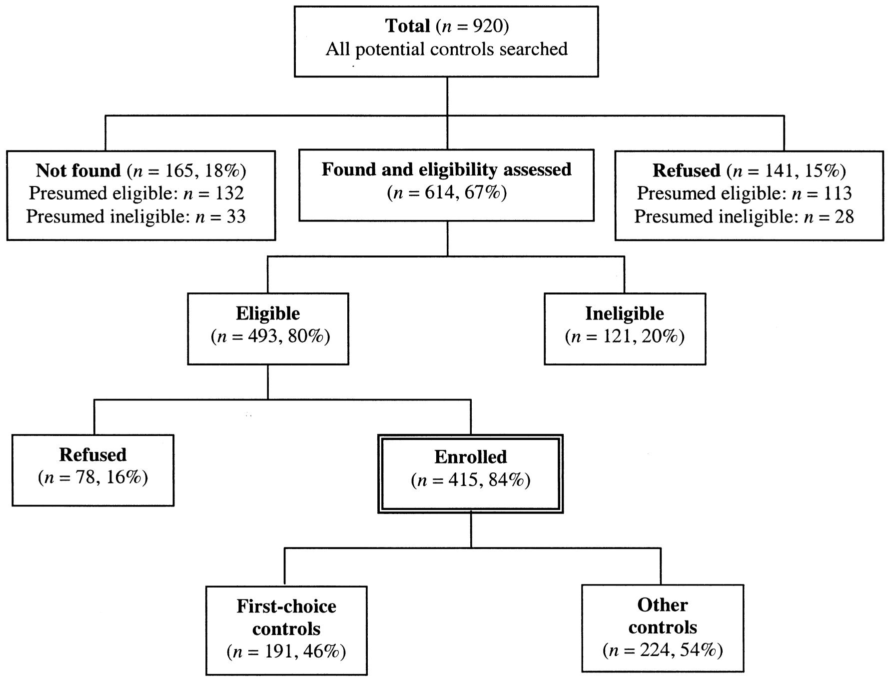

FIGURE 1. Control selection strategy for the child's diet analysis, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002. For controls "presumed eligible" and "presumed ineligible" in the "not found" and "refused" boxes at near-top left and right, respectively, the authors assumed that the same percentage would be eligible as for potential controls who were found and whose eligibility to participate in the study was assessed.

TABLE 1. Construction of food frequency categories for the first 2 years of life from food frequency categories for the first year and second year of life obtained from the child's diet questionnaire, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002

Food/food group	Original categories for first 2 years of life separately	New categories for the first 2 years of life combined		
		"Rare/no consumption"	"Occasional consumption"	"Regular consumption"
Hot dogs/lunch meats, beef/hamburger, orange juice, soda	Rarely or never, 1–3 days/week, 4–6 days/week, almost every day, twice a day, ≥3 times/day	Rarely or never for both periods	Rarely or never for one period and ≥1–3 days/week for the other period	≥1–3 days/week for both periods
Oranges/bananas, apples/grapes, fruit juice	Rarely or never, 1–3 days/week, 4–6 days/week, almost every day, twice a day, ≥3 times/day	Rarely or never for both periods; rarely or never for one period and ≥1–3 days/week for the other period; rarely or never for one period and ≥4–6 days/week for the other period	1–3 days/week for both periods; 1–3 days/week for one period and ≥4–6 days/week for the other period	≥4–6 days/week for both periods
Vegetables	Rarely or never, 1–3 days/week, 4–6 days/week, almost every day, twice a day, ≥3 times/day	Rarely or never for both periods	Rarely or never for one period and 1–3 days/week for the other period; rarely or never for one period and ≥4–6 days/week for the other period; 1–3 days/week for both periods; 1–3 days/week for one period and ≥4–6 days/week for the other period	≥4–6 days/week for both periods
Milk	Rarely or never, 1–3 days/week, 4–6 days/week, almost every day, twice a day, ≥3 times/day	Rarely or never for both periods	Rarely or never for one period and 4–6 days/week for the other period; rarely or never for one period and ≥3 times/day for the other period; 4–6 days per week for both periods; 4–6 days per week for one period and ≥3 times/day for the other period	≥3 times/day for both periods
Vitamins	No, yes	No for both periods	No for one period and yes for the other period	Yes for both periods

between individual foods/food groups and with income and education were evaluated with Pearson's correlation coefficients. Both univariable and multivariable logistic models were constructed and analyzed by conditional logistic regression techniques.

To measure the degree of association between frequency of consumption of each food/food group and risk of leukemia identified by the conditional logistic model, we utilized the likelihood ratio statistic and its associated two-sided p value. Odds ratios were considered to be consistent with statistical significance if the 95 percent confidence intervals excluded 1.00 and/or $p \leq 0.05$. Confounding was examined by comparing the odds ratios for the predictor variables in the models with and without inclusion of the confounding variables defined a priori as annual household income, maternal education, birth weight, and breastfeeding. The study population is ethnically diverse and comprises two distinct periods of data collection. Therefore, the presence of effect modification was examined by creating interaction terms for maternal Hispanic status, time from dietary intake to diagnosis using age at diagnosis (2–5 years and 6–14 years), and phase of data collection. Since all of the tests for interaction were not significant ($p \leq 0.20$), an additive conditional logistic model was assumed. Finally, goodness-of-fit of the model was assessed by calculating a Pearson chi-squared test statistic for quasi independence (19, 20).

RESULTS

All leukemia cases and controls were similar with respect to breastfeeding and birth weight (table 3). The leukemia cases came from families with lower annual household income ($p < 0.001$) and were born to mothers with fewer years of education ($p < 0.05$) compared with the controls. In addition, the study sample was ethnically diverse, consisting of about 37 percent Hispanic, 51 percent non-Hispanic White, 3 percent non-Hispanic Black, and 9 percent other. The subset of acute lymphoblastic leukemia cases and their matched controls exhibited similar characteristics to those of all the leukemia cases and their matched controls.

Almost all of the foods/food groups were significantly correlated with each other (table 4), with the exception of milk and vitamins, which were significantly associated with only hot dogs/lunch meats ($p < 0.05$). Intuitively related foods such as oranges/bananas, apples/grapes, and orange juice ($p < 0.001$) and hot dogs/lunch meats, beef/hamburger, and soda ($p < 0.001$) were significantly correlated with each other. Higher consumption of vegetables was negatively correlated with lower intake of soda ($p < 0.001$). In addition, markers of socioeconomic status, such as household income and maternal education, were negatively correlated with soda and orange juice consumption ($p < 0.05$) and positively correlated with vegetable consumption ($p < 0.05$) (not shown). Consumption of oranges/bananas and hot dogs/lunch meats was not significantly correlated with income ($p > 0.05$) and education ($p > 0.05$) (not shown).

Each food/food group was analyzed using separate univariable conditional logistic regression models. Oranges/bananas and vegetables were significantly associated with a reduced risk of childhood leukemia (not shown). Pearson's chi-squared goodness-of-fit test statistic for oranges/bananas ($\chi^2 = 0.03$; $p = 0.86$) and vegetables ($\chi^2 = 3.40$; $p = 0.07$) reflected an adequate fit of the data using the conditional logistic model.

Two multivariable models were constructed. In the first model, the odds of disease for each food/food group were analyzed with adjustment for birth weight, duration of breastfeeding, maternal education, and household income. In the second model, the odds of disease for each food/food group were examined with adjustment for the aforementioned covariates as well as for the other foods/food groups. Regular consumption of oranges/bananas during the first 2 years of life was associated with a reduced risk of childhood leukemia after adjusting for birth weight, breastfeeding, maternal education, and household income (odds ratio (OR) = 0.67, 95 percent confidence interval (CI): 0.42, 1.06; $p_{trend} = 0.06$) (table 2). Further adjustment for the other foods/food groups showed that regular consumption of oranges/bananas was associated with a significant reduction in risk of leukemia (OR = 0.49, 95 percent CI: 0.26, 0.94; $p_{trend} = 0.02$) (table 2). Consumption of orange juice was also associated with a significant reduction in risk of disease after adjusting for birth weight, breastfeeding, maternal education, and household income only (OR = 0.67, 95 percent CI: 0.43, 1.03; $p_{trend} = 0.07$) and with the other foods/food groups included (OR = 0.54, 95 percent CI: 0.31, 0.94; $p_{trend} = 0.04$) (table 2). When the models were restricted to cases diagnosed between the ages of 2 and 5 years and their matched controls, consumption of oranges/bananas and orange juice during the first 2 years of life was also associated with a reduced risk of leukemia, although the odds ratios were no longer significant (table 2). Analysis with only acute lymphoblastic leukemia cases and their matched controls yielded similar results (not shown), which is consistent with the peak incidence of acute lymphoblastic leukemia occurrence in children aged 2–5 years (4).

Finally, two multivariable models of foods/food groups consumed during the first year and second year of life, respectively, were developed. Consumption of oranges/bananas and orange juice during either time period was associated with a nonsignificant, reduced risk of childhood leukemia (not shown). Therefore, results from this more time-sensitive analysis reconfirmed the overall results depicted in table 2.

DISCUSSION

In this study, a protective association between consumption of oranges/bananas and orange juice during the child's early life and risk of childhood leukemia was elucidated. Specifically, regular consumption of oranges/bananas and orange juice during the first 2 years of life was associated with a reduced risk of leukemia in children diagnosed at less than 15 years of age. Similar results were found for children diagnosed between 2 and 5 years of age. Furthermore, when the foods/food groups consumed were examined for the first year and second year of life separately, the protective effect remained but was not significant. No association was apparent for consumption of hot dogs/lunch meats and risk of leukemia.

TABLE 2. Multivariable analysis of child's early diet prior to age 2 years and subsequent risk of childhood leukemia, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002

Consumption of food/ food group	Age 2–14 years*,†						Age 2–5 years*,‡					
			Model 1§		Model 2¶				Model 1§		Model 2¶	
	Cases (%)	Controls (%)	Odds ratio#	95% confidence interval#	Odds ratio	95% confidence interval	Cases (%)	Controls (%)	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Hot dogs/lunch meat												
Rare/no	44	48	1.00		1.00		41	46	1.00		1.00	
Occasional	44	40	1.17	0.82, 1.67	1.08	0.67, 1.72	44	46	1.19	0.75, 1.89	1.04	0.56, 1.95
Regular	12	12	1.15	0.65, 2.04	1.61	0.72, 3.58	15	12	1.32	0.66, 2.62	1.78	0.60, 5.27
p_{trend}			0.44		0.33				0.36		0.43	
Beef/hamburger												
Rare/no	38	36	1.00		1.00		37	36	1.00		1.00	
Occasional	44	47	0.89	0.61, 1.29	0.90	0.56, 1.44	42	47	0.69	0.42, 1.13	0.55	0.28, 1.06
Regular	18	17	1.08	0.67, 1.75	1.56	0.79, 3.06	21	17	1.19	0.64, 2.22	1.52	0.64, 3.60
p_{trend}			0.90		0.36				0.92		0.69	
Vegetables												
Rare/no	14	8	1.00		1.00		13	8	1.00		1.00	
Occasional	45	48	0.53	0.30, 0.94	0.64	0.31, 1.30	45	48	0.59	0.27, 1.27	0.76	0.29, 1.99
Regular	41	44	.57	0.31, 1.02	0.66	0.31, 1.40	42	44	0.62	0.29, 1.35	0.84	0.32, 2.24
p_{trend}			0.24		0.46				0.46		0.91	
Oranges/bananas												
Rare/no	25	21	1.00		1.00		25	20	1.00		1.00	
Occasional	50	47	0.96	0.63, 1.45	0.84	0.50, 1.42	51	49	0.89	0.52, 1.53	0.87	0.42, 1.79
Regular	25	32	0.67	0.42, 1.06	0.49	0.26, 0.94	24	31	0.67	0.37, 1.20	0.60	0.25, 1.43
p_{trend}			0.06		0.02				0.15		0.22	
Apples/grapes												
Rare/no	57	47	1.00		1.00		54	49	1.00			
Occasional	28	38	0.64	0.44, 0.92	0.86	0.54, 1.36	30	38	0.65	0.40, 1.06	0.88	0.47, 1.66
Regular	15	15	0.89	0.55, 1.43	0.94	0.47, 1.85	16	13	1.00	0.53, 1.90	0.98	0.37, 2.62
p_{trend}			0.19		0.66				0.51		0.85	

Table continues

The findings of a reduced risk of childhood leukemia associated with the consumption of oranges/bananas and orange juice are consistent with the protective role of fruits and/or vegetables observed in adults with solid tumors (1, 2) and more recently in adults with leukemia (3). Oranges and particularly bananas are popular fruits consumed regularly by the US population (21). Both fruits have a high content of vitamins and minerals; oranges and bananas are rich in vitamin C and potassium, respectively. Vitamin C is an antioxidant that may prevent oxidative damage to DNA, thus precluding initiating events in carcinogenesis (22). In addition, vitamin C may deactivate reactive metabolites in the stomach or duodenum and prevent the formation of mutagenic *N*-nitroso compounds (8). As for potassium, its role as an anticarcinogenic agent has been speculated upon by epidemiologists (23). The replacement of potassium ions with sodium ions in DNA and RNA nucleic acids may destabilize the genetic material and cause the formation of neoplasms (24). Indeed, negative correlations between potassium intake and cancer incidence have been shown in various animal and human studies (25). Furthermore, vitamin C and potassium could operate in conjunction to reduce the risk of cancer, since intake of vitamin C has been demonstrated to increase intracellular potassium intake (23).

Consumption of hot dogs/lunch meats was not associated with risk of childhood leukemia, thus lending no support to the *N*-nitroso hypothesis (5). In the NCCLS population, very few children ate hot dogs during their first year of life (only 40 of 324 cases and 47 of 415 controls), while more than half of the children ate hot dogs during their second year of life (182 of 322 cases and 213 of 411 controls). Since vitamin C has been postulated to hinder the production of *N*-nitroso compounds in the gut, it is possible that the consumption of oranges/bananas and orange juice inhibited this biologic reaction and prevented the formation of these carcinogenic agents.

Previous studies have not reported an association between consumption of fruits or fruit juices and risk of childhood leukemia and have produced mixed results regarding the association between consumption of hot dogs/lunch meats and risk of childhood leukemia. Peters et al. (12) analyzed 252 leukemia cases diagnosed from birth to age 10 years

TABLE 2. Continued

Consumption of food/ food group	Age 2–14 years*,†						Age 2–5 years*,‡					
	Cases (%)	Controls (%)	Model 1§		Model 2¶		Cases (%)	Controls (%)	Model 1§		Model 2¶	
			Odds ratio#	95% confidence interval#	Odds ratio	95% confidence interval			Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Orange juice												
Rare/no	42	37	1.00	0.64, 1.45	1.00	0.58, 1.58	43	36	1.00	0.54, 1.55	1.00	0.49, 1.90
Occasional	27	30	0.96		0.96		29	33	0.92		0.96	
Regular	31	33	0.67	0.43, 1.03	0.54	0.31, 0.94	28	31	0.56	0.31, 1.02	0.48	0.22, 1.06
p_{trend}			0.07		0.04				0.07		0.08	
Fruit juice												
Rare/no	26	28	1.00		1.00		30	30	1.00		1.00	
Occasional	29	31	1.17	0.76, 1.80	1.11	0.63, 1.96	29	32	0.89	0.51, 1.57	0.90	0.42, 1.91
Regular	45	41	1.24	0.81, 1.90	1.42	0.77, 2.62	41	38	1.16	0.66, 2.06	1.51	0.63, 3.65
p_{trend}			0.33		0.25				0.54		0.35	
Milk**												
Rare/no	8	9	1.00		1.00		8	8	1.00		1.00	
Occasional	47	54	0.70	0.20, 2.47	0.93	0.13, 6.88	47	54	1.02	0.17, 6.17	NC	NC
Regular	45	37	NC††	NC	NC	NC	45	38	NC	NC	NC	NC
p_{trend}			0.45		0.26				0.61		0.55	
Soda												
Rare/no	67	72	1.00		1.00		63	69	1.00		1.00	
Occasional	25	217	1.10	0.74, 1.62	0.91	0.55, 1.52	28	23	1.19	0.73, 1.96	0.92	0.47, 1.78
Regular	8	7	0.97	0.49, 1.92	1.31	0.53, 3.27	9	8	0.98	0.41, 2.34	1.80	0.53, 6.17
p_{trend}			0.83		0.84				0.70		0.63	
Vitamins												
Rare/no	37	37	1.00		1.00		38	41	1.00		1.00	
Occasional	23	21	1.20	0.76, 1.88	0.98	0.56, 1.73	23	25	1.14	0.65, 2.01	1.20	0.58, 2.48
Regular	40	42	0.88	0.59, 1.31	0.70	0.42, 1.18	39	34	1.15	0.68, 1.95	1.15	0.58, 2.28
p_{trend}			0.56		0.18				0.59		0.68	

* Age at diagnosis for cases and age at the corresponding date for controls.
† Age 2–14 years: cases (n = 328); controls (n = 415).
‡ Age 2–5 years: cases (n = 196); controls (n = 256).
§ Adjusted for birth weight (g), duration of breastfeeding (months), maternal education (categorical), and annual household income (categorical).
¶ Adjusted for the other foods/food groups in addition to the covariates specified in the § footnote above.
# Odds ratios and 95% confidence intervals derived from conditional logistic regression, which accounts for matching on child's date of birth, sex, Hispanic status, maternal race, and maternal county of residence at birth (only phase 1).
** Missing values for frequency of consumption of foods/food groups besides milk ranged from one to 17 observations. For milk consumption, 30 and 50 observations were missing for cases and controls, respectively (these children had not started drinking milk at the time of administration of the questionnaire).
†† NC, not calculable.

from the Los Angeles County Cancer Surveillance Program (1980–1987) and friend and random digit dialing controls matched on sex, age, and ethnicity to the cases. They found no evidence that fruit or fruit drinks reduced the risk of childhood leukemia but reported a significant odds ratio of 9.5 (95 percent CI: 1.6, 57.6) for child's consumption of 12 or more hot dogs a month versus none during the reference period. This odds ratio was based on only 14 exposed cases and three exposed controls.

In another study, Sarasua and Savitz (13) examined 56 acute lymphoblastic leukemia cases ascertained from the Colorado Central Cancer Registry (1976–1983) along with random digit dialing controls matched on age, sex, and telephone exchange to the cases. In addition, the controls were restricted to children who were residents of their homes on the date of the matched case's diagnosis until the time of their selection, thus creating a more residentially stable control group as compared with the case group. The effects of consumption of fruits or fruit juices on risk of childhood leukemia were not assessed in this study. Furthermore, no significant association was reported for eating any type of cured meat and risk of leukemia.

Several potential limitations of this study need to be evaluated prior to considering the causality of the results. First, the questionnaire administered to the respondents asked about oranges and bananas as one food group instead of as

TABLE 3. Selected characteristics of childhood leukemia cases and controls aged 2–14 years, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002

	All leukemia					Acute lymphoblastic leukemia				
	Cases		Controls		*p* value*	Cases		Controls		*p* value*
	No.	%	No.	%		No.	%	No.	%	
Child's age, years†										
2–5	196	60	256	62		186	65	244	67	
6–10	87	26	104	25		70	25	83	23	
11–14	45	14	55	13		29	10	39	10	
Mean (years)	6.02		5.91			5.91		5.79		
Child's sex†										
Male	178	54	221	53		152	53	191	52	
Female	150	46	194	47		133	47	175	48	
Child's race/ethnicity†										
Hispanic	120	37	155	37		106	38	138	38	
Non-Hispanic White	167	51	209	51		146	51	186	51	
Non-Hispanic Black	11	3	13	3		7	2	8	2	
Other	30	9	38	9		26	9	34	9	
Maternal education					<0.05					0.06
≤High school	145	44	149	36		124	44	128	35	
Some post-high school	90	28	142	34		81	28	129	35	
College graduate	92	28	0			79	28	109	30	
Unknown	1					1				
Annual household income, $					<0.001					<0.001
<15,000	47	14	36	9		39	14	31	8	
15,000–29,999	58	18	55	13		52	18	50	14	
30,000–44,999	55	17	50	12		47	17	42	12	
45,000–59,999	59	18	68	16		54	19	57	16	
60,000–74,999	35	11	59	14		29	10	49	13	
≥75,000	74	22	147	36		64	22	137	37	
Breastfeeding, months					0.57					0.59
Never	69	22	79	19		57	20	65	18	
≤6	148	46	186	45		130	47	167	46	
>6	103	32	146	36		92	33	132	36	
Unknown	8		4			6		2		
Mean (months)	6.22		6.52			6.52		6.59		
Birthweight, g					0.95					0.69
<2,500	17	5	18	4		17	6	16	4	
2,500–2,999	50	16	64	16		44	16	53	15	
3,000–3,499	108	34	141	35		99	36	128	36	
≥3,500	140	45	181	45		114	42	161	45	
Unknown	13		11			11		8		
Mean (g)	3,453.35		3,449.40			3,449.40		3,449.23		
Total	328‡		415‡			285§		366§		

* From Pearson's chi-squared test; two sided.

† Phase 1 (August 19, 1995–November 30, 1999): cases and controls matched on date of birth, sex, Hispanic status, maternal race, and maternal county of residence at birth. Phase 2 (December 1, 1999–November 30, 2002): cases and controls matched on date of birth, sex, Hispanic status, and maternal race. "Age" is age at diagnosis for cases and age at the corresponding date for controls.

‡ All leukemia: 241 case-control pairs, 1:1; and 87 case-control triplets, 1:2.

§ Acute lymphoblastic leukemia: 204 case-control pairs, 1:1; and 81 case-control triplets, 1:2.

TABLE 4. Pearson's correlation matrix of frequency of consumption of 10 foods/food groups during the first 2 years of life, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002*

	Hot dogs/ lunch meats	Beef/ hamburger	Vegetables	Oranges/ bananas	Apples/ grapes	Orange juice	Fruit juice	Milk	Soda	Vitamins
Hot dogs/lunch meats										
Pearson's *r*	1.00	0.36	0.10	0.10	0.10	–0.02	0.20	0.08	0.27	0.09
p value		<0.001	0.006	0.008	0.006	0.65	<0.001	0.04	<0.001	0.02
Beef/hamburger										
Pearson's *r*		1.00	0.15	0.10	0.14	0.06	0.12	0.05	0.17	0.0004
p value			<0.001	0.008	<0.001	0.10	0.001	0.21	<0.001	0.99
Vegetables										
Pearson's *r*			1.00	0.24	0.16	–0.05	0.14	0.07	–0.12	0.03
p value				<0.001	<0.001	0.18	0.001	0.08	<0.001	0.37
Oranges/bananas										
Pearson's *r*				1.00	0.42	0.19	0.27	0.05	0.01	–0.001
p value					<0.001	<0.001	<0.001	0.16	0.75	0.97
Apples/grapes										
Pearson's *r*					1.00	0.18	0.22	–0.01	0.11	0.02
p value						<0.001	<0.001	0.73	0.003	0.60
Orange juice										
Pearson's *r*						1.00	0.24	–0.007	0.12	0.03
p value							<0.001	0.87	0.001	0.40
Fruit juice										
Pearson's *r*							1.00	0.07	0.13	0.08
p value								0.07	<0.001	0.02
Milk										
Pearson's *r*								1.00	0.04	0.003
p value									0.27	0.94
Soda										
Pearson's *r*									1.00	0.01
p value										0.69
Vitamins										
Pearson's *r*										1.00

* All diet variables simultaneously analyzed as categorical variables on an ordinal scale. All foods/food groups were divided into the following frequency categories: 1 = "rare/no consumption"; 2 = "occasional consumption"; 3 = "regular consumption."

two separate foods. Consequently, the independent effects of oranges and bananas could not be separated in the analysis, and the observed association lacks specificity in that the reduced risk could be the result of vitamin C in oranges, potassium in bananas, or both nutrients combined. Considering that a similar reduction in risk was found for consumption of orange juice and that intakes of oranges/bananas and orange juice were significantly correlated, vitamin C might be the relevant exposure.

In addition, the initial evaluation of the child's diet was exploratory in design; therefore, an accurate assessment of the frequency of consumption of foods/food groups during the first 2 years of life in this study population has not been conducted. None of the published studies of childhood leukemia that have addressed dietary consumption have used validated questionnaires (12, 13). Regarding the reproducibility of results, the phase 1 and phase 2 data analyzed separately had similar point estimates for the foods/food groups (not shown). This internal reproducibility provides some evidence of consistency of results in this particular study population.

Lastly, an inherent problem of all case-control studies is recall bias. The respondents for cases could have recalled consumption of certain foods more readily than the respondents for controls or vice versa, thus producing differential misclassification. This bias was minimized by mailing preparatory materials to all the respondents prior to the in-home interview to act as a memory aide. Furthermore, there was no public perception at the time of data collection that child's diet is associated with leukemia risk. Finally, in terms of recall inaccuracy, exploration of effect modification by age at diagnosis showed no significant difference in odds of disease between children diagnosed earlier in life as compared with later in life.

The dietary assessment and study design of the NCCLS have several strengths. First and foremost, the questionnaire was designed to account for the timing of food exposures. Dietary consumption in two distinct and critical periods of the child's early development, the first year of life and the second year of life, was the main focus. During this time, significant immunologic changes are occurring in the child, especially with regard to gastric permeability (26, 27), that can evoke a local immune response. These responses could be related to leukemia risk either directly or by not being properly modulated by early exposures such as breastfeeding and infection (Greaves' hypothesis) (28, 29). Vitamin C may also play a critical role in protecting the child against early childhood infections through its antioxidative properties (22).

Second, the questionnaire was composed of an adequate list of foods that covered a broad spectrum of a typical young child's diet. Earlier studies focused too narrowly on foods primarily related to *N*-nitroso compounds and failed to include all foods likely to have been consumed (12, 13).

Finally, selection bias among controls is probably less of a concern despite the fact that income and education were higher in the controls as compared with the cases. Early ecologic and descriptive studies of childhood leukemia have reported higher socioeconomic status in cases compared with controls (30, 31). In contrast, more recent case-control studies of childhood leukemia have described higher socioeconomic status in controls compared with cases, an observation that might be attributable to selection bias (17, 32, 33). Overall, the role of socioeconomic status remains uncertain in the etiology of childhood leukemia, especially considering the difficulty in assessing socioeconomic status and disentangling the impact of bias. In an attempt to evaluate selection bias, an analysis of 64 matched birth certificate-friend control pairs from the NCCLS and 192 "ideal" population-based controls randomly chosen from birth records for the study area was conducted (18). Data on parental age, parental education, mother's reproductive history, and birth weight were compared. For all variables, the differences between participating birth certificate controls and "ideal" controls were smaller and nonsignificant as compared with those between participating friend controls and "ideal" controls. These results indicate that the NCCLS birth certificate controls are representative of the source population from which the cases arose. The modest participation rate in the NCCLS may raise some concern, but the participation rate is not the most relevant consideration for purposes of inference. The representativeness of the participating controls or comparability with the underlying study population is more important, and it appears that the NCCLS data satisfy this requirement.

In this analysis, no difference existed between cases and controls for breastfeeding and birth weight, contrary to many other childhood leukemia studies, but the evidence has not been entirely consistent (34, 35). For breastfeeding, the absence of an association might be due to the high prevalence (82 percent) of ever having breastfed in this unique study population. This high percentage is in marked contrast to the descriptive statistics derived from the Third National Health and Nutrition Examination Survey, which reported 54 percent of US infants ever being breastfed (36). The NCCLS birth weight data are consistent with null associations reported in a recent population-based study of birth characteristics and childhood leukemia in California (37). A strength of this study is that controls were randomly selected from state birth files rather than from recruited volunteers. Therefore, the possibility of selection bias was virtually eliminated. Additionally, previous studies of leukemia and birth weight have focused mainly on Caucasian children; thus, the ethnic diversity of the NCCLS population must be taken into consideration.

Overall, this study described a consistently decreased risk of childhood leukemia with regular reported consumption of oranges/bananas and orange juice during the first 2 years of life. The association with hot dogs/lunch meats and leukemia risk noted in earlier studies was not confirmed. The effect of oranges/bananas remained for foods consumed during the child's first year and second year of life after taking into consideration other foods/food groups in the child's diet, vitamin supplement intake, birth weight, breastfeeding, maternal education, and annual household income. In conclusion, these findings suggest that fruits or fruit juices with a high content of vitamin C and/or potassium may reduce the risk of childhood leukemia, especially if consumed regularly during the first 2 years of life. If these results are replicated in an independent study, the public health implications are profound and are just cause to initiate a feasible and inexpensive dietary intervention among young children involving regular consumption of fruits and fruit juices.

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