Food consumption of children and risk of childhood leukemia

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Summary

The possible relationship 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 two years) are associated with risk of childhood leukemia in a case-control study of a diverse California population. Dietary data were obtained by questionnaire administered to the child's caregiver. Conditional logistic regression was used to analyze 328 case-control sets matched on age, sex, maternal race, and parental Hispanic status. Regular consumption of oranges/bananas (odds ratio (OR) = 0.49; 95% confidence interval (CI) = 0.26, 0.94) and orange juice (OR = 0.54; 95% CI = 0.31, 0.94) during the first two years of life was associated with a reduction in risk of childhood leukemia diagnosed between the ages of 2 to 14. Restricting the analysis to leukemia diagnosed between the ages of 2 to 5 reflected a similar pattern of reduced risk. No association between eating hotdogs/lunchmeats 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 consumed on a regular basis during the first two years of life.

Introduction

Nutrition has been implicated in possibly reducing the risk of adult solid tumors such as colorectal, prostate, lung, and breast (Steinmetz and Potter, 1991, Block *et al.* 1992), and its association with adult leukemia has only been recently shown for vegetable intake (Ross *et al.* 2002). 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 (Smith *et al.* 1999), 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 (Preston-Martin *et al.* 1982, Preston-Martin and Lijinsky, 1994). 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 (Mirvish, 1983). 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 (Blot *et al.* 1999). 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 (Rice *et al.* 1989). 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 (Tannenbaum and Mergens, 1980). This hypothesis can be extended to other childhood cancers such as leukemia and lymphoma (Blot *et al.* 1999). Only one study has examined consumption of cured meats and leukemia risk and reported a significant increased risk for child's consumption of 12 or more hotdogs a month versus none (Peters *et al.* 1994).

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

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: Phase one from August 19, 1995 to November 30, 1999 and Phase two from December 1, 1999 to November 30, 2002. During Phase one, the study area encompassed 17 counties in the greater San Francisco-Oakland Bay Area while during Phase two, the area expanded to 35 counties including the Central Valley of California. After each case was identified, a control subject was selected from birth certificates through the California Office of Vital Records. Birth certificates were matched either 1:1 or 1:2 to the case on age, sex, maternal race, maternal or paternal Hispanic status, and maternal county of residence at birth (only Phase one). This analysis utilized 241 pairs and 87 triplets. The overall case and control participation rates were 86 and 56 percent, respectively.

Data collection and management

During Phase one, child's dietary data were collected by a mailed questionnaire that was completed by the biological mother before the in-home interview. During Phase two, child's dietary data were gathered by a questionnaire that was completed by the biological mother after the in-home interview. The questionnaire asked about the frequency of consumption of nine foods/food groups during the child's first and second year of life: hotdogs/lunchmeats, beef/hamburger, vegetables, oranges/bananas, apples/grapes, orange juice, fruit juice, milk and soda. Frequency categories on the questionnaire were collapsed into simpler categories for both the first and second years of life in order to eliminate small numbers of observations. To summarize food consumption over the first two years of life, new categories of "Rare/no consumption," "Occasional consumption," and "Regular consumption" were created based on the original categories.

Statistical analysis

Sociodemographic characteristics of cases and controls were compared using the Pearson chi-square test. Correlations between individual foods/food groups and with income and education were evaluated with Pearson correlation coefficients. Both univariable and multivariable logistic models were constructed and analyzed by conditional logistic regression techniques.

To measure the degree of association between consumption of each food/food group and risk of leukemia identified by the conditional logistic model, the likelihood ratio statistic and its associated two-sided *p* value were utilized. Odds ratios (OR) were considered to be consistent with statistical significance if the 95% confidence intervals (CI) excluded 1.00 and/or the *p* value ≤ 0.05. Confounding was examined by comparing the ORs for the predictor variables in the models with and without inclusion of the confounding variables defined *a priori* as annual household income, maternal education, birthweight, and breastfeeding. The presence of effect modification was examined by creating interaction terms for maternal Hispanic status, time from dietary intake to diagnosis using age of diagnosis (2 to 5 years and 6 to 14 years), and phase of data collection. Since all of the tests for interaction were not significant ($p \geq 0.20$), an additive conditional logistic model was assumed. The power to detect a difference in risk of OR = 0.70 at an alpha level of 0.05 and exposure prevalence of either 0.4 or 0.5 was 0.59 (one control) and 0.71 (two controls), respectively, and 0.62 (one control) and 0.75 (two controls), respectively.

Results

Intuitively related foods such as oranges/bananas, apples/grapes, and orange juice ($p < 0.001$) and hotdogs/lunchmeats, beef/hamburger, and soda ($p < 0.001$) were significantly correlated with each other (table 1). Higher consumption of vegetables was negatively correlated with lower intake of soda ($p < 0.001$).

Table 1. Pearson correlation matrix* of frequency of consumption of selected foods/food groups during the first two years of life assessed in the child's diet questionnaire of the NCCLS (1995-2002)

	Hotdogs†	**Beef†**	**Vegetables†**	**Oranges/ Bananas†**	**Apples/ Grapes†**	**Orange Juice†**	**Soda†**
Hotdogs†	1.00	0.36 (<0.001)	0.10 (0.006)	0.10 (0.008)	0.10 (0.006)	-0.02 (0.65)	0.27 (<0.001)
Beef†	---	1.00	0.15 (<0.001)	0.10 (0.008)	0.14 (<0.001)	0.06 (0.10)	0.17 (<0.001)
Vegetables†	---	---	1.00	0.24 (<0.001)	0.16 (<0.001)	-0.05 (0.18)	-0.12 (<0.001)
Oranges/ Bananas†	---	---	---	1.00	0.42 (<0.001)	0.19 (<0.001)	0.01 (0.75)
Apples/ Grapes†	---	---	---	---	1.00	0.18 (<0.001)	0.11 (0.003)
Orange Juice†	---	---	---	---	---	1.00	0.12 (0.001)
Soda†	---	---	---	---	---	---	1.00

* Each cell contains a Pearson correlation coefficient *r* and its two-sided *p* value in parentheses.

† All diet variables simultaneously analyzed as categorical variables on an ordinal scale. All foods/food groups were divided into three categories: 1 = "Rare/no consumption", 2 = "Occasional consumption", and 3 = "Regular consumption".

Two multivariable models were constructed. In the first model, the odds of disease for each food/food group was analyzed after adjusting for birthweight, duration of breastfeeding, maternal education, and household income. In the second model, the odds of disease was examined with adjustment for the above covariates as

well as for the other foods/food groups. Regular consumption of oranges/bananas during the first two years of life was associated with a reduced risk of childhood leukemia (OR = 0.67; 95% CI: 0.42, 1.06) (table 2, model 1). Further adjustment for the other foods/food groups showed that regular consumption of oranges/bananas was associated with a significant reduction in leukemia risk (OR = 0.49; 95% CI: 0.26, 0.94) (table 2, model 2). Consumption of orange juice was also associated with a significant reduction in risk of disease (OR = 0.67; 95% CI: 0.43, 1.03) (table2, model 1) and with the other foods/food groups included (OR = 0.54; 95% CI: 0.31, 0.94) (table 2, model 2). When the models were restricted to cases diagnosed between age two to five and their matched controls, intake of oranges/bananas and orange juice during the first two years of life was associated with a reduced risk, although the ORs were no longer significant (not shown).

Table 2. Multivariable analysis of child's early diet prior to age two years and subsequent risk of childhood leukemia (NCCLS, 1995-2002)

Consumption of Food/Food Group*	Cases n (%)	Controls n (%)	Model 1*		Model 2†	
			OR‡	95% CI‡	OR	95% CI
Hotdogs/Lunchmeats						
Rare/no	140 (44)	198 (48)	1.00		1.00	
Occasional	141 (44)	166 (40)	1.17	0.82, 1.67	1.08	0.67, 1.72
Regular	39 (12)	47 (12)	1.15	0.65, 2.04	1.61	0.72, 3.58
			p trend = 0.44		*p* trend = 0.33	
Oranges/Bananas						
Rare/no	82 (25)	88 (21)	1.00		1.00	
Occasional	162 (50)	194 (47)	0.96	0.63, 1.45	0.84	0.50, 1.42
Regular	78 (25)	132 (32)	0.67	0.42, 1.06	0.49	0.26, 0.94
			p trend = 0.06		*p* trend = 0.02	
Orange Juice						
Rare/no	131 (42)	151 (37)	1.00		1.00	
Occasional	85 (27)	120 (30)	0.96	0.64, 1.45	0.96	0.58, 1.58
Regular	98 (31)	132 (33)	0.67	0.43, 1.03	0.54	0.31, 0.94
			p trend = 0.07		*p* trend = 0.04	

* Adjusted for birthweight (grams), 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 *****.

‡ OR, odds ratio; CI, confidence interval. OR and CI derived from conditional logistic regression, which accounts for matching on child's date of birth, sex, maternal race, maternal or paternal Hispanic status, and maternal county of residence at birth (only Phase one).

Discussion

A protective association was reported between consumption of oranges/bananas and orange juice during the child's early life and risk of childhood leukemia. Specifically, regular consumption of oranges/bananas and orange juice during the first two years of life was associated with a reduced risk of leukemia in children diagnosed less than 14 years of age. Similar results were found for children diagnosed between two to five years of age. No association was apparent for consumption of hotdogs/lunchmeats and risk of leukemia.

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 (Steinmetz and Potter, 1991, Block *et al.* 1992) and more recently in adults with leukemia (Ross *et al.* 2002). Oranges and particularly bananas are popular fruits consumed regularly by the U.S. population (Pollack, 2001). 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 (Padayatty *et al.* 2003). In addition, vitamin C may deactivate reactive metabolites in the stomach or duodenum and prevent the formation of mutagenic *N*-nitroso compounds (Blot *et al.* 1999). As for potassium, its role as an anti-carcinogenic agent has been speculated upon by epidemiologists (Jansson, 1990). 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 (Pantellini, 1976). Indeed, negative correlations between potassium intake and cancer incidence have been shown in various animal and human studies (Jansson, 1996). 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 (Jansson, 1990).

Consumption of hotdogs/lunchmeats was not associated with risk of childhood leukemia, thus lending no support to the *N*-nitroso hypothesis (Preston-Martin *et al.* 1982). In the NCCLS population, very few

children ate hotdogs during their first year of life (12% of cases and 11% of controls) while more than half of the children ate hotdogs during their second year of life (57% of cases and 52% of controls). Since vitamin C has been postulated to hinder the production of *N*-nitroso compounds in the gut, it is possible that consumption of oranges/bananas and orange juice might have prevented the formation of these carcinogenic agents.

Conclusions

Overall, this study described a consistently decreased risk of childhood leukemia with regular reported consumption of oranges/bananas and orange juice during the first two years of life. The association with hotdogs/lunchmeats and leukemia risk noted in earlier studies was not confirmed. The oranges/bananas effect 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, birthweight, breastfeeding, maternal education, and annual household income. In the future, the frequency of consumption of oranges and bananas will be collected in the questionnaire separately and then analyzed. In conclusion, these results 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 two 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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