

## Maternal dietary risk factors in childhood acute lymphoblastic leukemia (United States)

Christopher D. Jensen<sup>1,\*</sup>, Gladys Block<sup>1</sup>, Patricia Buffler<sup>1</sup>, Xiaomei Ma<sup>2</sup>, Steve Selvin<sup>1</sup>, & Stacy Month<sup>3</sup> representing the Northern California Childhood Leukemia Study Group

<sup>1</sup>School of Public Health, University of California, Berkeley, CA, USA; <sup>2</sup>Yale University School of Medicine, USA;

<sup>3</sup>Kaiser Permanente, Oakland, CA, USA

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### Abstract

**Objective:** Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, and the second most common cause of mortality in children aged 1–14 years. Recent research has established that the disease can originate *in utero*, and thus maternal diet may be an important risk factor for ALL.

**Methods:** The Northern California Childhood Leukemia Study is a population-based case–control study of risk factors for childhood leukemia, including maternal diet. Cases ( $n = 138$ ) and controls ( $n = 138$ ) were matched on sex, date of birth, mother's race, Hispanicity, and county of residence at birth. Maternal dietary intake in the 12 months prior to pregnancy was obtained by a 76-item food frequency questionnaire.

**Results:** Consumption of the vegetables (OR = 0.53; 95% CI, 0.33–0.85;  $p = 0.008$ ), protein sources (OR = 0.40; 95% CI, 0.18–0.90,  $p = 0.03$ ), and fruits (OR = 0.71; 95% CI, 0.49–1.04;  $p = 0.08$ ) food groups were inversely associated with ALL. Among nutrients, consumption of provitamin A carotenoids (OR = 0.65, 95% CI, 0.42–1.01;  $p = 0.05$ ), and the antioxidant glutathione (OR = 0.42; 95% CI, 0.16–1.10;  $p = 0.08$ ) were inversely associated with ALL.

**Conclusion:** Maternal dietary factors, specifically the consumption of vegetables, fruits, protein sources and related nutrients, may play a role in the etiology of ALL. Dietary carotenoids and glutathione appear to be important contributors to this effect.

### Introduction

The leukemias of childhood account for the largest number of cases of childhood cancer and are the primary cause of cancer-related mortality of children in the United States<sup>[1]</sup>. Approximately 3250 children under age 20 years are diagnosed with leukemia each year, of which about 2400 cases are acute lymphoblastic leukemia (ALL) [1]. With the exception of rare causes such as high doses of ionizing radiation and specific genetic syndromes, the etiology is unknown. However, evidence has accumulated within the last few years that the initiating genetic event in

leukemia development often occurs *in utero*. Through analysis of blood samples obtained at birth, it has been demonstrated that leukemia clone-specific, non-constitutive chromosomal translocations are present at birth in children subsequently diagnosed with leukemia [2–5]. These findings underscore the importance of examining potential risk factors in the *in utero* environment.

The effect of maternal diet on childhood leukemia risk has not been rigorously studied and prior studies have all been limited by incomplete assessment of maternal diet [6–10]. Of five prior studies, three involved very limited assessment of dietary factors [6–8], and two examined medication and vitamin supplement use during pregnancy [9, 10], but did not assess dietary intake. Maternal consumption of cured meat is a potential risk factor of interest because of animal studies showing that transplacental exposure to *N*-nitroso precursor compounds, found in cured meats, produces a very high incidence of brain tumors in the offspring of exposed mothers [11].

\* Address for correspondence to: Christopher D. Jensen, PhD, 419 Warren Hall, University of California, Berkeley, CA 94720-7360, USA. Ph.: +1-510-643-1875; Fax: +1-510-643-6981; E-mail: cjensen@berkeley.edu

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However, two studies found no statistically significant associations of maternal cured meat consumption with ALL [6,8], while a third found a positive association with hot dog consumption that was of borderline statistical significance [7]. The most notable findings of prior studies were inverse associations between ALL and maternal use of supplements containing folic acid with or without iron [10], and cod liver oil containing vitamins A and D [9]. Finally, maternal consumption of topoisomerase II inhibitor foods was associated with an increase risk of acute myeloid leukemia in infants, but was not associated with infant ALL [8].

The Northern California Childhood Leukemia Study (NCCLS) is a population-based matched case-control study of risk factors for childhood leukemia. It is the first to include a comprehensive assessment of maternal dietary intake including supplement use, thus allowing a thorough examination of diet-disease relationships. *A priori* hypothesized risk factors include maternal exposure to cured meats, vitamin supplement use, intake of specific food groups and nutrients, and consumption of topoisomerase II inhibitor foods.

## Materials and methods

### Study population

In the NCCLS, incident cases were identified using rapid case ascertainment, from pediatric oncology centers in the Northern California region. Although case ascertainment was hospital-based, comparison with cases ascertained by the California Cancer Registry (1997-1999) showed that over 88% of newly diagnosed cases in the San Francisco - Oakland Metropolitan Statistical Area were identified by our study methods. Cases were eligible if they were under 15 years of age, had a parent who spoke English or Spanish, were resident in the study area at the time of diagnosis, and had no prior cancer diagnosis. The research 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.

Controls were identified from birth certificates, matched to the case on date of birth, sex, maternal race (White, African American, other), Hispanic ethnicity of mother or father, and county of residence at birth. If the case child was not born in California (< 10% of cases), potential controls were selected from the case's county of residence at diagnosis.

Of eligible cases identified during the initial five-year period of the study (January 1, 1995 to November 30,

1999), 83% consented to participate. Among the eligible controls approached, 69% consented to participate. There were 161 cases of ALL and matched birth-certificate controls who provided dietary information. Seven pairs in which a respondent was not the biological mother were excluded, since we wished to make inferences regarding the effect of the *in utero* environment. From the remaining 154 pairs, we deleted 16 pairs in which a case and/or control dietary questionnaire contained questionable data (more than 10 foods skipped, one pair; mother's consumption of fewer than two or more than 17 solid foods per day, 10 pairs; energy estimate greater than 4500 kcal, five pairs). The final analytic sample thus includes 138 matched pairs of cases and birth certificate controls, representing credible dietary questionnaires from biological mothers of children with ALL and their matched controls.

### Data collection

Maternal dietary intake was obtained by interview, using a modified version of the Block food frequency questionnaire (FFQ) [12-14]. The time frame covered was the year before the index pregnancy. This time period was chosen rather than diet during pregnancy, because it would represent the probable state of nutritional adequacy at the start of the pregnancy. Furthermore, diet during pregnancy varies by trimester and the degree of nausea, and may be more difficult to report accurately than would the time frame immediately prior to pregnancy. In addition, it appears that unlike *quantity* of food consumed (which does increase during pregnancy), dietary *composition* and habitual patterns such as frequent or infrequent consumption of vegetables are fairly consistent from before to during pregnancy. This is supported by data from Bunin (G. Bunin, personal communication, 2002), who administered a FFQ focused on diet in the year before pregnancy and another in mid-pregnancy focused on diet in the second trimester. Correlations between the two nutrient estimates (before and during pregnancy) averaged  $r = 0.89$  for macronutrients and fats, and  $r = 0.87$  for vitamins and minerals from food. Thus, we believe that our questionnaire provides indirect information about diet during pregnancy as well information about nutritional status in the pre- and periconception periods.

The mother was also asked whether she ate more, the same, or less during her pregnancy for selected food groups including fruits and vegetables. To evaluate the effect of possible changes in intake during pregnancy, revised estimates for fruit and vegetable intake were calculated by increasing (or decreasing) the frequency of consumption by one-half of a standard deviation for

responses 'much more' or 'much less', or by one-fourth of a standard deviation for responses 'somewhat more' or 'somewhat less'.

The FFQ took approximately 20 minutes to administer, and contained 76 food items, as well as questions on vitamin supplement usage, use of certain reduced-fat foods, and cooking fat types (see Appendix 1 for a list of foods included). Food items were selected by identifying the top population contributors of each nutrient, separately in Whites, African Americans and Hispanics, in the Third National Health and Nutrition Examination Survey (NHANES III). Frequency of consumption was reported in nine categories, ranging from 'never or less than once per month' to two or more per day. Portion size was obtained for each food, using three-dimensional abstract models. The 76 food items were selected to be representative of a wide range of dietary factors including total calories, macronutrients, fiber, vitamins, minerals, antioxidants including carotenoids, and phytoestrogens. In addition, cured meats and other foods were included to address prior hypotheses. The vitamin supplement questions asked about two types of multiple vitamins and nine single vitamins, and information was obtained on frequency and duration and, for vitamins C and E, usual daily dose.

A Spanish version of the FFQ was developed, to include not only culturally appropriate translations of the English version, but also additional foods important in the diets of the Latina population. To identify these foods, two surveys were examined, the Third National Health and Nutrition Examination Survey (NHANES III) and the Hispanic Health and Nutrition Examination Survey (HHANES) [15–17]. In addition, information from focus groups of Latinas in the San Francisco Bay area was used. This process resulted in the addition of seven foods (evaporated/condensed milk; green peppers/chile rellenos; avocado/guacamole; chili peppers; mole/sofrito sauces; corn tortillas; flour tortillas.) These items were added only to the Spanish version of the FFQ, as previous research has shown that inclusion of ethnic-specific foods in a questionnaire for Caucasians adds to burden but makes no meaningful contribution to intake or to ranking [18]. The questionnaire was administered by bilingual interviewers.

Dietary nutrients were calculated using the BlockSys program [13] by multiplying frequency of consumption of each food by its nutrient content and reported portion size, and summing over all foods. Nutrients obtained from vitamin supplements were estimated by multiplying the frequency of consumption of each type (multiple vitamins, specific single vitamins) times the amount of the nutrient in typical compositions of each type. For vitamins E and C, usual dose was obtained

from subjects who took those vitamins. Frequency of consumption of food groups was calculated by summing the reported frequency for all foods in a food group. Macro- and micronutrient estimates from Block questionnaires have been subjected to numerous validation studies and found to produce good point estimates and rankings in relation to a variety of reference data [19–21]. A validation of retrospective assessment of diet before and during pregnancy has been conducted by Bunin *et al.*, who found correlations of the Willett FFQ with reference data to be similar to those obtained for current diet [22].

### Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated from conditional logistic regression to describe the association between the nutritional factor and risk of ALL [23]. Variables were log-transformed to improve normality and reduce skewness.

Potential confounding variables considered *a priori* were birth weight, breastfeeding, maternal age and education, parental occupation, and smoking during pregnancy. However, no evidence of confounding was observed for these variables. Variables previously shown to be significantly associated with ALL risk in the NCCLS study (income, prior fetal loss, child's exposure to other children under age five, and maternal exposure to indoor insecticides during pregnancy) were included in the final conditional logistic regression model, along with portion size and energy consumption.

A combined exposure variable for consumption of topoisomerase II inhibitor foods was calculated from intake of foods from the fruits, vegetables, and beans food groups (Appendix 1), as well as wine or wine coolers, and black or green tea. Frequency of consumption for foods was scored as follows: 'Never or less than once per month' = 1; '1 per month' = 2; '2–3 per month' = 3; '1 per week' = 4; '2 per week' = 5; '3–4 per week' = 6; '5–6 per week' = 7; and 'every day' = 8. For beverages, frequency of consumption was scored as follows: 'Never or less than once per month' = 1; '1–3 times per month' = 2; 'Once per week' = 3; '2–4 times per week' = 4; '5–6 times per week' = 5; '1 per day' = 6; '2–3 per day' = 7; '4 per day' = 8; and '5+ per day' = 9. The scores were summed for each subject and the combined exposure score was included in the model as a continuous variable.

### Results

Mean age at diagnosis for cases was  $5.2 \pm 3.48$  years and 77% of the matched pairs were between the ages of

Table 1. Selected characteristics of cases, controls, and mothers, n = 138 matched pairs

	Cases n (%)	Controls n (%)	p-value <sup>a</sup>
Case/control age at case diagnosis (years)			
< 2	16 (11.6%)	16 (11.6%)	
2–10	106 (76.8%)	106 (76.8%)	
> 10	16 (11.6%)	16 (11.6%)	
Case/control sex			
Female	63 (45.7%)	63 (45.7%)	
Male	75 (54.3%)	75 (54.3%)	
Maternal age (years)			0.63
< 20	8 (6%)	9 (6%)	
20–24	27 (20%)	23 (15%)	
25–29	37 (27%)	39 (31%)	
30–34	46 (33%)	41 (30%)	
≥35	20 (14%)	26 (18%)	
Mean (SE)	29 (0.47)	30 (0.51)	
Maternal Education			0.46
≤High school	48 (35%)	42 (30%)	
Some college	45 (33%)	47 (34%)	
≥Bachelor's degree	45 (33%)	49 (36%)	
Household income			< 0.01
Under 15,000	13 (9%)	12 (9%)	
15,000–29,000	27 (20%)	13 (9%)	
30,000–44,000	21 (15%)	13 (9%)	
45,000–59,000	18 (13%)	19 (14%)	
60,000–74,000	18 (13%)	21 (15%)	
75,000+	41 (30%)	60 (43%)	

<sup>a</sup> Based on Mantel-Haenszel Chi Square.

two and 10 years (Table 1). Cases and controls consisted of 45.7% females and 54.3% males. The sample of mothers was ethnically diverse, consisting of 60% non-Hispanic White, 28% Hispanic, 1% non-Hispanic Black, and 11% other ethnic groups. Cases and controls were similar with respect to maternal age and maternal education. Household income tended to be higher in controls than in cases ( $p < 0.01$ ).

As this is the first study to comprehensively assess maternal diet in childhood leukemia, we sought to explore associations between consumption of various dietary factors and disease risk, including food groups, specific foods, a broad range of nutrients, and associations seen in past studies such as consumption of cured meats, vitamin supplement use, and topoisomerase II inhibitor foods.

#### Food groups and component foods

Food groups examined were vegetables, fruits, dairy foods, beans, protein sources, grains, alcoholic beverages, and a group consisting of fats, oils, sweets, and snacks (Table 2). These food groups correspond to the food groups found in the United States Department of

Table 2. Food group results: means and odds ratios for acute lymphoblastic leukemia in relation to pre-pregnancy maternal diet, 138 matched pairs<sup>a</sup>

Variables (times/day)	Sample mean (SD)	Adjusted OR <sup>b</sup> (95% CI)	p-value
Vegetables	0.74 (0.48)	0.53 (0.33–0.85)	0.008
Fruit	0.78 (0.58)	0.71 (0.49–1.04)	0.08
Grain products	2.68 (1.10)	0.86 (0.37–1.98)	0.72
Dairy products	2.17 (1.33)	1.16 (0.78–1.72)	0.48
Protein sources	1.85 (0.83)	0.40 (0.18–0.90)	0.03
Cured meat	0.60 (0.37)	0.71 (0.44–1.15)	0.16
Fats, sweets, snacks	3.21 (1.78)	1.18 (0.67–2.06)	0.57

<sup>a</sup> Food groupings are listed in Appendix 1.

<sup>b</sup> Separate models for each food group and odds ratios calculated using log-transformed values. Adjusted for energy intake, income, previous miscarriages or stillbirths, hours the child was exposed to other children at preschools, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra large.

Agriculture Food Guide Pyramid [24], and their component foods are listed in Appendix 1. Maternal consumption of vegetables (OR = 0.53; 95% CI, 0.33–0.85) and protein sources (OR = 0.40; 95% CI, 0.18–0.90) were both inversely associated with ALL and statistically significant. Fruit consumption (OR = 0.71; 95% CI, 0.49–1.04) was also inversely associated with disease and borderline statistically significant ( $p = 0.08$ ). Consumption of other food groups were not found to be statistically significant risk factors.

Among the vegetables and fruit food groups (Table 3), consumption of carrots (OR = 0.79; 95% CI, 0.67–0.94) and string beans or peas (OR = 0.84; 95% CI, 0.71–1.00) were inversely associated with disease and statistically significant. Consumption of cantaloupe was inversely associated with disease and of borderline statistical significance (OR = 0.87; 95% CI, 0.75–1.02;  $p = 0.095$ ). Among the protein sources food group (Table 4), beans (OR = 0.83; 95% CI, 0.70–0.99), and beef (OR = 0.80; 95% CI, 0.66–0.99) were inversely associated with disease and statistically significant.

#### Macronutrients and micronutrients

Odds ratios for consumption of macronutrients and total micronutrients (diet and vitamin supplement use) are shown in Table 5. Consumption of total vitamin A (OR = 0.58; 95% CI, 0.32–0.98) and its precursors, provitamin A carotenoids (OR = 0.65; 95% CI, 0.42–1.01) and alpha carotene (OR = 0.67; 95% CI, 0.49–0.90) were inversely associated with disease and statistically significant. Borderline significant inverse associations were seen for consumption of beta carotene (OR = 0.67; 95% CI, 0.43–1.04;  $p = 0.07$ ) and reduced glutathione (OR = 0.42; 95% CI,

Table 3. Vegetables and fruit food group results: means and odds ratios for acute lymphoblastic leukemia in relation to pre-pregnancy maternal diet, 138 matched pairs

Food (times/day)	Sample mean (SD)	Adjusted OR <sup>a</sup> (95% CI)	<i>p</i> -value
Tomatoes, tomato juice	4.24 (2.17)	0.94 (0.82–1.08)	0.39
Coleslaw, cabbage	2.07 (1.51)	0.88 (0.71–1.08)	0.22
Mustard greens, turnip greens, collards, kale	1.23 (0.80)	0.88 (0.58–1.34)	0.56
Carrots, or mixed vegetables containing carrots	4.14 (1.86)	0.79 (0.67–0.94)	0.009
Broccoli	3.72 (1.81)	1.00 (0.84–1.19)	0.98
Spinach	2.18 (1.51)	1.02 (0.81–1.27)	0.90
String beans or peas	3.40 (1.81)	0.84 (0.71–1.00)	0.048
Cauliflower or Brussels sprouts	2.13 (1.49)	1.03 (0.83–1.27)	0.81
Peaches, apricots, canned/dried	2.11 (1.58)	1.03 (0.86–1.23)	0.73
Peaches, apricots, fresh	3.68 (2.19)	0.98 (0.86–1.12)	0.76
Oranges or grapefruit	4.30 (2.16)	0.91 (0.79–1.04)	0.17
Mangoes or papayas	2.20 (2.03)	0.90 (0.77–1.06)	0.22
Cantaloupe	3.30 (1.89)	0.87 (0.75–1.02)	0.095
Bananas	4.57 (1.81)	0.99 (0.85–1.16)	0.92
Apples, applesauce	4.13 (2.01)	0.99 (0.87–1.12)	0.84

<sup>a</sup> Separate models for each food and odds ratios calculated using log-transformed values. Adjusted for energy intake, income, previous miscarriages or stillbirths, hours the child was exposed to other children at preschools, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra large.

0.16–1.10; *p* = 0.08). Only saturated fat consumption had an odds ratio substantially above 1 (OR = 1.69; 95% CI, 0.58–4.96; *p* = 0.34) but it was not statistically significant.

#### Non-users of vitamin supplements

Because diet–disease relationships might be different in non-users of vitamin supplements, the food group, macronutrient, and micronutrient analyses above were repeated among 66 matching case–control pairs who did not use vitamin supplements. However, the directions of the associations were similar to those reported overall (data not shown in tables). Consumption of protein sources (OR = 0.18; 95% CI, 0.04–0.76; *p* = 0.02) and total glutathione (OR = 0.15; 95% CI, 0.02–0.96; *p* = 0.046) were inversely associated with disease and statistically significant. Among dietary factors with borderline statistically significant associations, consumption of dairy foods was positively associated with ALL (OR = 1.68; 95% CI, 0.92–3.07; *p* = 0.09), whereas consumption of alpha carotene (OR = 0.66; 95% CI, 0.42–1.05; *p* = 0.08), reduced glutathione (OR = 0.19; 95% CI, 0.03–1.07; *p* = 0.06), and

Table 4. Protein foods group results: means and odds ratios for acute lymphoblastic leukemia in relation to pre-pregnancy maternal diet, 138 matched pairs

Food (times/day)	Sample mean (SD)	Adjusted OR <sup>a</sup> (95% CI)	<i>p</i> -value
Tofu	1.36 (1.05)	1.00 (0.76–1.31)	0.97
Peanuts, peanut butter	2.99 (1.89)	1.00 (0.86–1.18)	0.97
Beans	4.14 (2.07)	0.83 (0.70–0.99)	0.03
Eggs	3.99 (1.67)	0.99 (0.83–1.18)	0.90
Cured meats			
Sausage or bacon	2.73 (1.57)	0.87 (0.71–1.08)	0.20
Hot dogs	1.93 (1.15)	0.80 (0.60–1.07)	0.13
Ham, bologna, other lunch meat	3.29 (2.03)	0.91 (0.78–1.07)	0.25
Oysters	1.11 (0.44)	1.00 (0.52–1.94)	0.99
Fried fish	1.64 (1.13)	0.97 (0.82–1.30)	0.82
Fish, broiled or baked	2.11 (1.40)	1.03 (0.71–1.08)	0.22
Fried chicken	2.27 (1.59)	0.95 (0.77–1.17)	0.64
Chicken, broiled or baked	4.01 (1.83)	0.93 (0.78–1.10)	0.39
Pork	2.83 (1.47)	0.91 (0.74–1.11)	0.35
Hamburger, ground	3.96 (1.78)	0.90 (0.75–1.09)	0.28
Beef	3.85 (1.63)	0.80 (0.66–0.99)	0.04
Liver	1.24 (0.73)	0.83 (0.53–1.31)	0.43

<sup>a</sup> Separate models for each food and odds ratios calculated using log-transformed values. Adjusted for energy intake, income, previous miscarriages or stillbirths, hours the child was exposed to other children at preschools, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra large.

selenium (OR = 0.13; 95% CI, 0.016–1.08; *p* = 0.06) were inversely associated with disease.

#### Cured meats

Maternal consumption of individual cured meats (Table 4), as either hot dogs, sausage and bacon, lunch meats (which included ham, bologna, other lunch meats, regular or made with turkey), or total cured meats (Table 2), were inversely associated with disease, but none achieved statistical significance. Consumption of vitamin C and E can block nitrosation reactions and have been shown to prevent brain tumor formation in the offspring of pregnant animals fed N-nitroso precursors [11]. Therefore, we examined the interaction of cured meat consumption and intake of vitamins C and E (from diet and supplements), however, the consumption of these nutrients did not modify the disease risk associated with cured meat consumption (data not shown).

#### Vitamin supplement usage

The food frequency questionnaire included questions about use of multiple vitamin supplements, multiple

Table 5. Nutrient Results: means and odds ratios for acute lymphoblastic leukemia in relation to pre-pregnancy maternal diet, 138 matched pairs

Nutrient (unit)	Mean Intake/day (SD)	Adjusted OR <sup>a</sup> (95% CI)	p-value
Energy (kcal)	2118.9 (812.5)	0.61 (0.25–1.49)	0.28
Protein (g)	82.9 (34.2)	0.64 (0.19–2.17)	0.47
Total fat (g)	92.6 (39.0)	1.13 (0.30–4.18)	0.86
Saturated fat (g)	30.2 (14.0)	1.69 (0.58–4.96)	0.34
Monounsaturated fat (g)	34.3 (15.1)	0.96 (0.32–2.86)	0.94
Polyunsaturated fat (g)	19.5 (8.6)	1.02 (0.41–2.55)	0.97
Cholesterol (mg)	266.1 (121.6)	1.00 (0.47–2.12)	0.99
Carbohydrate (g)	245.9 (106.6)	0.41 (0.09–1.88)	0.25
Dietary fiber (g)	18.0 (9.3)	1.00 (0.96–1.04)	0.92
Vitamins			
Vitamin A (RE) (total)	1497.1 (1110.6)	0.58 (0.32–0.98)	0.04
Retinol ( $\mu$ g)	522.4 (358.0)	1.12 (0.70–1.80)	0.64
Thiamin (B1) (mg) (total)	1.8 (0.8)	0.72 (0.33–1.59)	0.42
Riboflavin (B2) (mg) (total)	2.1 (1.0)	0.97 (0.48–1.94)	0.92
Niacin (mg) (total)	21.3 (9.3)	0.79 (0.38–1.67)	0.54
Folic acid ( $\mu$ g) (total)	348.0 (187.4)	0.78 (0.33–1.81)	0.56
Vitamin B6 (mg) (total)	2.0 (0.9)	0.84 (0.41–1.75)	0.65
Vitamin B12 ( $\mu$ g)	4.7 (2.7)	0.86 (0.45–1.65)	0.65
Vitamin C (mg) (total)	153.3 (101.7)	1.00 (0.64–1.57)	0.99
Vitamin D (mg) (total)	226.0 (219.0)	1.02 (0.75–1.39)	0.90
Vitamin E (aTE) (total)	10.6 (4.2)	1.01 (0.66–1.55)	0.96
Minerals			
Calcium (mg) (total)	971.4 (556.5)	0.99 (0.48–2.04)	0.97
Zinc (mg) (total)	11.7 (5.7)	0.85 (0.47–1.54)	0.60
Zinc from animal sources (mg)	7.0 (4.4)	0.92 (0.53–1.62)	0.80
Iron (mg) (total)	15.5 (8.1)	0.89 (0.51–1.53)	0.66
Magnesium (mg) (total)	296.7 (131.8)	0.66 (0.23–1.95)	0.46
Sodium (mg)	2603.7 (1052.4)	0.29 (0.05–1.84)	0.19
Potassium (mg)	3238.6 (1404.7)	0.55 (0.13–2.32)	0.42
Selenium ( $\mu$ g)	99.3 (39.1)	0.41 (0.10–1.65)	0.21
Carotenoids			
Provitamin A carotenoids ( $\mu$ g)	5810.4 (6141.2)	0.65 (0.42–1.01)	0.05
Alpha-carotene ( $\mu$ g)	1031.1 (1406.8)	0.66 (0.49–0.90)	0.008
Beta-carotene ( $\mu$ g) (total)	3664.4 (3827.8)	0.70 (0.47–1.06)	0.09
Cryptoxanthin ( $\mu$ g)	170.1 (175.3)	0.97 (0.79–1.19)	0.77
Lutein ( $\mu$ g)	1756.4 (2280.1)	0.86 (0.59–1.26)	0.45
Lycopene ( $\mu$ g)	6447.0 (4992.4)	0.98 (0.73–1.30)	0.88
Daidzein ( $\mu$ g)	460.9 (2072.0)	1.05 (0.93–1.17)	0.46
Genistein ( $\mu$ g)	960.3 (4282.7)	1.04 (0.94–1.16)	0.47
Glutathione (total) (mg)	53.3 (23.3)	0.48 (0.17–1.32)	0.15
Glutathione (reduced) (mg)	34.6 (15.7)	0.42 (0.16–1.10)	0.08

<sup>a</sup> Separate models for each nutrient and odds ratios calculated using log-transformed values. Adjusted for energy intake, income, previous miscarriages or stillbirths, hours the child was exposed to other children at preschools, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra large.

antioxidant supplements, and single supplements containing vitamin A, beta-carotene, vitamin C, vitamin E, calcium, iron, zinc, and selenium. Consumption of individual micronutrients from supplements only were not associated with ALL. Odds ratios were all close to 1.0 (ranging from 0.89 to 1.00) and none were statistically significant. The odds ratio corresponding to regular use of any vitamin supplement in the year prior to the index pregnancy was inversely related to

disease, but was not statistically significant (OR = 0.63; 95% CI, 0.21–1.94;  $p = 0.42$ ).

#### *Topoisomerase II inhibitor foods*

The dietary questionnaire included questions about consumption of a number of topoisomerase II inhibitor foods including a variety of vegetables, fruits, beans, tofu, meat substitutes from soy, soy beverages, wine or

wine coolers, and green or black tea. Aside from carrots, string beans or peas, and beans as noted above, none of these foods individually was associated risk of disease. When included in the model as a log-transformed combined exposure variable, consumption of topoisomerase II inhibitor foods was inversely associated with disease risk (OR = 0.37; 95% CI, 0.11–1.26;  $p = 0.11$ ), but did not achieve statistical significance. When only vegetables and fruits were included in the combined exposure variable, the inverse association was slightly stronger and statistically significant (OR = 0.33; 95% CI, 0.11–0.95;  $p = 0.04$ ).

#### Confounding by income

To address the possibility of incomplete control of confounding by income, the data were reexamined in the subset of 36 pairs who were exactly concordant on income category. As expected with a smaller sample size the confidence intervals were wider. However, the odds ratios for consumption of vegetables (OR = 0.69; 95% CI, 0.28–1.68;  $p = 0.41$ ) and fruits (OR = 0.84; 95% CI, 0.44–1.62;  $p = 0.60$ ) were still inverse but weaker, while the odds ratio for consumption of protein sources (OR = 0.36; 95% CI, 0.09–1.52;  $p = 0.16$ ) was slightly more strongly inverse. The odds ratio for glutathione consumption (OR = 0.43; 95% CI, 0.09–2.02;  $p = 0.28$ ) was very similar to that seen in the whole sample, and alpha-carotene (OR = 0.44; 95% CI, 0.21–0.90;  $p = 0.02$ ) was stronger and achieved statistical significance, in this sample of 36 pairs.

#### Dietary changes during pregnancy

The food frequency questionnaire included questions about changes in consumption of vegetable and fruit food groups during pregnancy. To address the effect of possible dietary changes during pregnancy, results were reexamined after adjusting the fruit and vegetable estimates for reported increases or decreases in intake during pregnancy. The odds ratio for fruit intake was unchanged. The odds ratio for vegetable consumption was lowered slightly, from OR = 0.53 to 0.45, and remained statistically significant (95% CI, 0.24–0.85;  $p = 0.01$ ). The dietary questionnaire did not include questions about changes in the consumption of protein sources during pregnancy.

#### Discussion

These data suggest that maternal consumption of vegetables, fruit, and protein sources prior to and

during pregnancy may lower the risk of having a child who develops ALL. The data are most consistent for consumption of vegetable and protein sources. Within these three food groups, consumption of carrots, string beans or peas, cantaloupe, beans, and beef were inversely related to disease.

These findings may be etiologically relevant in light of mounting evidence that the initiating genetic event in the development of leukemia, chromosomal translocation, frequently occurs *in utero* [2–5]. Fetal exposure to nutritional factors, through maternal diet, could be involved in the disease process by preventing an initial oxidative lesion in DNA, or through DNA repair mechanisms. The observed inverse associations of vegetable and fruit intake with ALL is consistent with the large body of epidemiologic evidence for inverse risk associations with vegetable and fruit intake for cancers of the mouth, pharynx, esophagus, lung, stomach, colon, and rectum [25–28]. This study now extends this inverse association of vegetable and fruit consumption to childhood ALL.

Among the vegetables food group, the strongest inverse association was for carrots, and in the fruits group, cantaloupe. There are numerous bioactive compounds in vegetables and fruit, including micronutrients, fiber, and various phytochemicals, and their separate or combined effects might contribute to the ability of these foods to reduce cancer risk. Carrots and cantaloupe, for example, are rich sources of provitamin A carotenoids, and consistent with this fact, consumption of provitamin A carotenoids, alpha carotene, and beta carotene were found to be inversely related to ALL in the study. Antioxidant micronutrients like carotenoids may protect against oxidative damage to biomolecules, such as lipids, lipoproteins and DNA, and thus influence the risk for cancer development. Indeed, prevention of DNA damage and enhanced DNA repair has been demonstrated after supplementation with fruit, juices, and several carotenoids [29–33]. Other postulated cancer-preventive mechanisms for diets rich in carotenoids include beneficial effects on immune function, cell transformation and differentiation, and cell-to-cell communication [34].

Consumption of cruciferous vegetables, such as broccoli, cauliflower, Brussels sprouts, cabbage, and greens are inversely associated with certain cancers and may act by influencing the activity of xenobiotic-metabolizing enzymes [34]. However, in our study we found no association between consumption of broccoli, cauliflower, or Brussels sprouts and ALL risk. Other putative nutritional risk factors for cancer, including maternal consumption of dietary fiber, whole grains, alcohol, total fat, and types of fat were not significantly related to disease risk in this study.

We unexpectedly observed that consumption of the protein sources food group, and beans and beef in particular, were inversely associated with disease risk. In searching for possible etiologically important constituents of these foods, we found that the antioxidant tripeptide glutathione, found in both meat and vegetable protein sources such as legumes, was inversely associated with disease. Circulating reduced glutathione is an important physiologic antioxidant that functions in the synthesis and repair of DNA, and plays a critical role in the detoxification of harmful compounds and the recycling of vitamins C and E to their reduced forms [35]. Cells of the human gastrointestinal tract have glutathione uptake mechanisms [36], although, short-term studies of the ability of dietary glutathione to raise circulating blood glutathione levels in humans have been conflicting [37]. Nonetheless, it is intriguing that the inverse association observed was even stronger in non-users of supplements whose overall dietary antioxidant status might be lower, and therefore, more dependent on the antioxidant effects of circulating glutathione. This may be a chance finding, but it is also possible that dietary glutathione may play a protective role. This would be appropriate to explore further in future epidemiologic studies of diet and cancer.

This study used an extensive dietary questionnaire designed to assess a wide range of food groups and nutrients, whereas most previous research has focused on only a small group of food types (Table 6). In previous research focused on cured meats and precursors or inhibitors of nitrosation, Peters *et al.* [7] found hot dogs to be positively associated with risk of leukemia, and of borderline statistical significance ( $p = 0.1$ ). In contrast, Sarasua and Savitz [6] found no association with maternal intake of five kinds of cured meat, and Ross *et al.* [8] found no association with maternal intake of total cured meats. In our data there was no evidence of increased risk associated with consumption of individual or total cured meats. Furthermore, there was no evidence that total intake of nitrosation inhibitors, vitamins C and E, modified disease risk.

In studies of supplement use during pregnancy, Shu *et al.* [9] found a reduced risk of childhood ALL associated with long-term usage of cod liver oil containing vitamins A and D, and Thompson *et al.* [10] found a reduced risk of ALL with maternal use of folate supplements with or without iron. In addition, *in vitro* data have suggested leukemia cell growth suppression by vitamin C [38], quercetin [39], and citrus bioflavonoids [40]. Our research shows significant risk reduction associated with total vitamin A and provitamin A consumption but not intake of retinoic acid, which

would be the vitamin A source in cod liver oil. Furthermore, our study provided no evidence of significant risk reduction associated with maternal pre-pregnancy intake of total vitamin D or folate (diet plus supplements), nor with consumption of any type of supplements including those containing folate or vitamin C. We were not able to examine risk associated with intake of quercetin or citrus bioflavonoids as the nutrient database used for the analysis of the childhood leukemia questionnaire did not include these dietary factors.

The majority of infant leukemias present with an abnormality involving the *MLL* gene on chromosome band 11q23 [8]. Similar abnormalities involving 11q23 have been observed in secondary acute myeloid leukemias that have followed administration of the chemotherapeutic agent epipodophyllotoxin as a treatment for certain malignancies. Epipodophyllotoxins inhibit DNA topoisomerase II, an enzyme found in actively dividing cells. Topoisomerase II inhibitors also exist in certain foods and Ross *et al.* found that among infants 12 months of age or less, maternal consumption of topoisomerase II inhibitor foods was associated with an increased risk of acute myeloid leukemia (OR = 10.2; 95% CI, 1.1–96.4), although it should be noted that the lowest exposure group included only four cases. They observed an inverse association with ALL, but it was not statistically significant (OR = 0.5; 95% CI, 0.2–1.4) [8]. In our sample which was composed entirely of ALL cases, we had few infant case-control pairs ( $n = 16$  less than two year of age). However, among the overall sample we found consumption of topoisomerase II inhibitor foods to be inversely associated with risk of ALL, an effect primarily attributable to vegetable and fruit consumption. These findings are consistent with what has been observed in infants with ALL [8]. Further studies are needed to clarify the role of maternal consumption of topoisomerase II inhibitor foods in infant acute myeloid leukemia.

Several limitations of these data should be considered. As in all dietary data, dietary factors are correlated with one another to some extent. Thus, caution is warranted in attributing risk or benefit to any particular food or nutrient. Our data collection focused on maternal diet immediately preceding pregnancy, and may have the greatest implications for maternal nutritional status early in pregnancy. However, Bunin (G. Bunin, personal communication, 2002) has shown that diet in the year before pregnancy is highly correlated with diet in mid-pregnancy. Therefore, we believe our dietary estimates exclusive of supplements (food groups, macronutrients, amino acids, glutathione) may be reasonable proxies of diet composition during pregnancy as well, and thus

Table 6. Studies of maternal diet and risk of childhood leukemia.

Author, year (reference), study location	Number of:		Age of cases, year	Period, Source	Dietary Assessment Method	Association with Leukemia
	Cases	Controls				
Sarasa, 1994 [6], Colorado	56 with ALL	206 matched on age, gender, telephone exchange	0–14	1976–1983, P	6-item questionnaire on cured meats, hamburger, charcoal broiled foods, vitamin supplement use	Ham, bacon, sausage, OR = 1.5 ns Hot dogs, OR = 0.9 ns Lunch meats, OR = 1.0 ns Hamburgers, OR = 1.2 ns Charbroiled foods, OR = 1.0 ns <i>Odds ratios tended to increase for cured meat consumption among those not taking vitamin supplements</i>
Peters, 1994 [7], Southern California	232 with mostly ALL	232 matched on age, gender, ethnicity	0–10	1980–1987, P	12-item questionnaire on cured meats, hamburger, charcoal broiled meats, fruits and juices, milk, coffee, colas	Ham, bacon, sausage, OR = 1.0 ns Hot dogs, OR = 2.4 ns Lunch meats, OR = 1.3 ns Hamburgers, OR = 1.2 ns Charbroiled meats, OR = 0.9 ns Fruits and juices, OR = 0.8–1.1 ns Cola drinks, OR = 1.0 ns Dairy foods, OR = 0.7–1.4 ns Eggs, OR = 2.1 ns Beans, AML OR = 8.8* Fish, ALL OR = 0.2* Fresh vegetables, OR = 2.8* Fresh vegetables, AML OR = 13.7* Canned vegetables, OR = 1.0 ns Fruit, AML OR = 4.6 <i>p</i> = 0.05 Milk, ALL OR = 0.3* Poultry, OR = 2.0 ns Cured meats, OR = 1.0 ns Regular meats, OR = 1.3 ns Soy, OR = 0.6 ns Regular coffee, OR = 2.5* Decaffeinated coffee, OR = 1.5 ns Teas, OR = 0.6–1.9 ns Cocoa, OR = 1.5 ns Alcoholic beverages, OR = 0.8–1.0 ns Vitamin A supplements, OR = 2.9 ns Topoisomerase II inhibitor foods, Overall OR = 1.1 ns ALL OR = 0.5 ns AML OR = 10.2*
Ross, 1996 [8], United States	84 (54 with ALL and 30 with AML)	97 matched on age, race, geography	< 12.5 months	1985–1995, H	27-item questionnaire on dairy foods, meats, fruits, vegetables, beverages, vitamin A supplements	Cod liver oil with vitamins A and D, Overall OR = 0.3* ALL OR = 0.4*
Shu, 1988 [9], Shanghai, China	309 (56% ALL)	618 matched on age, gender	0–15	1974–1986 P	In-person interview on a variety of factors including medication and supplement use during pregnancy	Folate with or without iron, OR = 0.4* Iron alone, OR = 0.75 ns
Thompson, 2001 [10], Western Australia	83 with common ALL	166 matched on age, gender, region	0–14	1984–1992, P	In-person interview on a variety of factors including medication and supplement use during pregnancy	

*Abbreviations:* ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; P, population registry; H, hospital files; ns: not statistically significant,

\* statistically significant at  $p < 0.05$ ; period refers to years over which cases were ascertained.

those results may be generalizable to pregnancy diets. Nonetheless, it is possible that dietary changes during pregnancy that were not accounted for may be important risk factors. In contrast to diet, vitamin supplement usage does increase during pregnancy, and our pre-

pregnancy results for vitamins and minerals provided by supplements may not apply to the possible role of those factors during pregnancy. Thus, the possible effects of supplements of vitamins A and D, folate, and antioxidants during pregnancy requires further research.

Another caution is the possibility of chance findings that could result from multiple comparisons. This study involved a comprehensive examination of maternal diet and analysis of multiple *a priori* hypotheses. As the study was designed to be hypothesis generating, statistical significance was not adjusted for multiple comparisons. In addition, the findings of a reduced risk associated with the consumption of the protein sources group was not predicted, and the inverse association observed for consumption of glutathione resulted from a *post hoc* analysis. It is also possible that other constituents of the protein sources food group, or an unknown confounder, could be the true etiologic agent.

Measurement error is a problem in all research requiring self-reports. In these results, the likely effect of random error is to bias the results toward the null. The possibility of recall bias cannot be ruled out, but there have been no widely-known hypotheses about the possible role of maternal dietary factors in childhood leukemia that might lead to recall bias. There are general hypotheses about a healthy diet, which could have led case mothers to underreport their vegetable and fruit intake; however, it is difficult to imagine that this would also be true for reported consumption of meats and other protein sources.

Some effect of selection bias in controls cannot be ruled out, inasmuch as controls tended to have higher income than cases. A selection that favored controls with higher income and education could tend to produce an apparently protective effect of vegetables, since higher SES is associated with higher consumption of fruits and vegetables [41, 42]. However, it would be unlikely to produce a protective effect of protein sources (meats, beans), which are not more frequently consumed among more affluent or well-educated groups [43]. In addition, such a selection bias should also have produced an apparently protective effect of vitamins, since the more affluent and well educated do take more vitamin supplements [44, 45]; however, we did not find vitamins to be protective. In addition, not only did we control for income, but cases and controls were matched on Hispanic ethnicity and were well balanced on maternal education, important determinants of dietary practices. Also, the vegetable and protein sources findings were still inverse when we repeated the analysis in income-concordant pairs, and indeed the odds ratio for alpha-carotene was more strongly inverse than in the overall analyses, and was significant even in that small subset of income-concordant pairs. Thus, case/control differences in income or education cannot wholly explain the observed reduced risk associated with vegetable and protein sources consumption. Finally, sample size

may be a limitation, particularly for a heterogeneous disease like childhood ALL which likely has a different etiology depending on age at diagnosis. The total of 138 case-control pairs may have limited the ability to tease out important risk factors.

A number of strengths of the study deserve mention. The use of birth certificate controls, and the matching on race and Hispanic ethnicity, reduced some of the biases that can be a problem in other recruitment designs. Extensive non-dietary data were obtained, including previous fetal losses, exposure to other children at an early age, maternal and paternal smoking, and household pesticide exposures, and were adjusted for when appropriate. The dietary data were given high priority in terms of interview time and study commitment, and the extensive food list was designed to assess a wide range of nutrients and food groups. Such dietary methodology should enhance future studies of childhood cancer.

In summary, we found maternal intake of vegetables, fruits, and protein sources to be inversely associated with childhood ALL. Consumption of carrots, string beans or peas, cantaloupe, beans, and beef were the specific foods inversely associated with disease. Consumption of provitamin A carotenoids, alpha and beta carotene, and reduced glutathione were the nutrients inversely associated with disease. These data add to the extensive body of evidence suggesting that diets rich in vegetables and fruit may reduce cancer risk. It should be noted that the estimated effects of vegetable and fruit consumption on cancer prevention have been smaller in prospective studies than estimated in case-control studies, and that cause and effect cannot be concluded from this study. Nonetheless, it would be prudent for women to consume a diet rich in vegetables and fruit prior to and during pregnancy. Finally, future research should examine whether dietary glutathione is inversely associated with cancer risk as we have observed.

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## Appendix 1. Foods on the NCCLS Food Frequency Questionnaire

*Vegetable group*

String beans or peas  
Broccoli  
Tomatoes, tomato juice  
Spinach, cooked or raw  
Mustard greens, turnip greens, collards, kale  
Carrots, or mixed vegetables containing carrots  
Cole slaw, cabbage  
Cauliflower or Brussels sprouts  
Cooked green peppers, chile rellenos<sup>a</sup>  
Chili peppers, hot chili sauce<sup>a</sup>

*Fruit group*

Bananas  
Apples, applesauce  
Peaches, apricots, canned or dried  
Peaches, apricots, fresh  
Cantaloupe  
Mangoes or papayas  
Oranges or grapefruit, not including juice

*Dairy group*

Cheese or cheese spreads  
Whole milk or chocolate whole milk  
2% milk or chocolate 2% milk  
Skim milk, 1% milk  
Yogurt, frozen yogurt  
Instant breakfast milk shakes like Carnation, or drinks like Sego, Ensure or Boost  
Pizza  
Cheese dishes without tomato sauce like macaroni and cheese  
Evaporated or condensed milk<sup>a</sup>

*Beans group*

String beans or peas  
Beans such as baked beans, kidney beans, or in chili or bean burritos or soup  
Tofu, bean curd  
Soy milk  
Peanuts, peanut butter

*Protein sources group (USDA Food Guide Pyramid definition) \**

Hamburgers, cheeseburgers, beef burritos or tacos  
Beef, including roasts, steaks, or in stir-fry or sandwiches  
Pork, including chops, roasts, or in stir-fry  
Fried chicken  
Chicken or turkey, roasted or broiled  
Fried fish or fish sandwich  
Other fish, broiled or baked  
Oysters  
Liver, including chicken livers  
Hot dogs, including turkey or chicken  
Ham, bologna, other lunch meats, regular or made with turkey  
Beans such as baked beans, kidney beans, or in chili or bean burritos or soup  
Eggs, not including Egg Beaters  
Sausage or bacon  
Tofu, bean curd  
Peanuts, peanut butter

*Grain group*

Rice or dishes made with rice  
Spaghetti, lasagna, other pasta with tomato sauce  
Cheese dishes without tomato sauce, like macaroni and cheese

## Pizza

Fiber cereals like raisin bran, granola or shredded wheat  
Other cold cereals like corn flakes or Cheerios  
Cooked cereals like oatmeal, oat bran, or grits  
Bagels, English muffins, hamburger buns  
Biscuits, muffins  
Bread, including white bread, French, whole wheat  
Corn bread, corn muffins  
Corn tortillas<sup>a</sup>  
Flour tortillas<sup>a</sup>

*Fats, oils, sweets, snacks group*

Margarine  
Butter  
Salty snacks, like potato chips or corn chips, popcorn, crackers  
Salad dressing and mayonnaise  
Ice cream  
Doughnuts, pastry, cookies or granola bars  
Chocolate candy, candy bars  
Cream, half & half or non-dairy creamer  
Sugar or honey

*Alcohol group*

Beer  
Wine or wine coolers  
Liquor or mixed drinks

*Miscellaneous (not in above groups)*

Tea, regular black tea or Chinese tea, not herbal teas  
Kool-Aid, Hi-C, or other drinks with added vitamin C  
Glasses of water  
Orange juice or grapefruit juice  
Apple juice, grape juice  
Salsa, ketchup, taco sauce  
Green salad  
French fries and fried potatoes  
White potatoes not fried, including boiled, baked, mashed  
Sweet potatoes, yams  
Meat substitutes made from soy, like soy burgers  
Chicken stew, chicken casserole or stir-fry  
Beef or vegetable stew or pot pie  
Vegetable soups  
Sauces such as mole, sofrito<sup>a</sup>  
Guacamole, avocado<sup>a</sup>

<sup>a</sup> On Spanish version of FFQ only.

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