Maternal Diet and Risk of Childhood Acute Lymphoblastic Leukemia

Marilyn L. Kwan, PhD[a]
Christopher D. Jensen, PhD, MPH[b]
Gladys Block, PhD[b]
Mark L. Hudes, PhD[c]
Lisa W. Chu, PhD[c]
Patricia A. Buffler, PhD, MPH[b]

SYNOPSIS

Objective. Intrauterine environmental factors, including maternal diet, may play an etiologic role in acute lymphoblastic leukemia (ALL), a common childhood cancer. Expanding on previous findings from phase 1 of the Northern California Childhood Leukemia Study (NCCLS), a population-based case-control study, we sought to further elucidate and replicate the relationships between maternal diet and ALL risk.

Methods. We matched 282 case-control sets of children (205 pairs and 77 triplets) from phases 1 and 2 of the NCCLS on sex, date of birth, mother's race, Hispanic racial/ethnic status, and county of residence at birth. We used an interviewer-administered food frequency questionnaire to obtain information on maternal dietary intake in the 12 months prior to pregnancy.

Results. Risk of ALL was inversely associated with maternal consumption of vegetable (adjusted odds ratio [AOR] = 0.65, 95% confidence interval [CI] 0.50, 0.84); protein sources (AOR=0.55, 95% CI 0.32, 0.96); fruit (AOR=0.81, 95% CI 0.65, 1.00); and legume food groups (AOR=0.75, 95% CI 0.59, 0.95). The risk reduction was strongest for consumption of the protein sources and vegetable food groups, independent of the child's diet up to age 2 years, and consistent across phases 1 and 2 of data collection for vegetable consumption.

Conclusions. These data suggest that it may be prudent for women to consume a diet rich in vegetables and adequate in protein prior to and during pregnancy as a possible means of reducing childhood ALL risk in their offspring.

[a]Kaiser Permanente, Division of Research, Oakland, CA

[b]University of California, School of Public Health, Berkeley, CA

[c]University of California, Department of Nutritional Sciences and Toxicology, Berkeley, CA

[c]Cancer Prevention Fellowship Program, Office of Preventive Oncology, National Cancer Institute, National Institutes of Health, Bethesda, MD

Address correspondence to: Marilyn Kwan, PhD, Kaiser Permanente, Division of Research, 2000 Broadway, Oakland, CA 94612; tel. 510-891-3521; fax 510-891-3106; e-mail <Marilyn.L.Kwan@kp.org>.

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Childhood leukemia is the primary cause of cancer-related mortality of children in the United States.[1] Of children with leukemia, 78% are diagnosed with acute lymphoblastic leukemia (ALL), the etiology of which is largely unknown.[2,3] However, as summarized by Maia et al.,[4] observations on clonal markers in leukemic cells from monozygotic twins concordant for leukemia, and evaluation of neonatal blood spots for clonotypic fusion gene sequences have provided compelling evidence that a substantial portion of childhood ALLs originate *in utero*, and that chromosome translocations are very early or initiating events.[4] These findings underscore the need to examine potential risk factors in the fetal environment, such as maternal diet.

In a previous report of 138 case-control pairs from phase 1 of the Northern California Childhood Leukemia Study (NCCLS), maternal consumption of the vegetable and protein sources food groups was inversely associated with offspring ALL.[5] Expanding on this research, we undertook a comprehensive analysis of 282 case-control sets from phases 1 and 2 of the NCCLS to further elucidate and replicate the relationships between maternal diet and ALL risk. Our analyses also took into account the potential confounding effect of the child's early diet, which has recently been reported to be associated with childhood acute leukemia risk.[6] We hypothesized that maternal diet is associated with offspring risk of ALL, independent of the child's early diet, and that observed relationships would be consistent across phase 1 and 2 data.

METHODS

Study population

The NCCLS is a matched case-control study, and the analysis presented in this article consisted of data collected from August 19, 1995, to November 30, 1999 (phase 1), and from December 1, 1999, to November 30, 2002 (phase 2). We identified incident leukemia cases on the basis of *International Classification of Diseases for Oncology, Third Edition* criteria,[7] using a rapid case-ascertainment procedure from pediatric hospitals in the northern and central California study region. During phase 1, the study area encompassed seven pediatric hospitals in 17 counties in the greater San Francisco-Oakland Bay area. During phase 2, the study area expanded to encompass nine pediatric hospitals and 35 counties including the Central Valley of California. Comparison with the statewide California Cancer Registry for 2000 showed that the NCCLS protocol identified 95% of eligible cases among residents in the five-county San Francisco-Oakland metropolitan statistical area and 76% of eligible cases in the other 30 counties of the study area. We considered case subjects to be eligible if they were younger than 15 years of age, had no prior cancer diagnosis, lived within the study region, and had parents who spoke either English or Spanish. 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 approved the study. We obtained written informed consent from parents of all participating children.

After identifying each case, we selected control subjects from birth certificates through the California Office of Vital Records, and matched the control subjects 1:1 (phase 1) or 1:2 (phase 2) to the case subjects on date of birth, sex, Hispanic status (if either parent was Hispanic, then we considered the child Hispanic), maternal race/ethnicity, and maternal county of residence at birth (phase 1 only; matching on maternal county of residence at birth was not continued in phase 2 because of concerns regarding overmatching on potential environmental exposures related to leukemia risk). For the 7% of case children not born in California, we selected controls from the case child's county of residence at diagnosis. Out-of-state case children were comparable to case children born in California on age, sex, Hispanic status, and maternal race. For each case subject, we identified four or more potential control subjects from the California birth registry and then randomized the control subjects for selection. If the first-choice control subject could not be located, was ineligible, or refused to participate, we then contacted the next randomly ordered control subject until an eligible control subject agreed to participate.[8]

As of December 1, 2002, we had obtained data from 866 individuals, including 283 leukemia case-control pairs matched 1:1 and 100 case-control triplets matched 1:2. The overall participation rate was 86% for cases (83% in phase 1 and 89% in phase 2) and 56% for controls (49% in phase 1 and 64% in phase 2). The reasons for nonparticipation among control subjects included refusal (26%) and unable to contact (18%). We excluded a total of 190 participants for the following reasons: leukemia diagnosis was not ALL (n=127), there were no dietary data (n=4), a case or control respondent was not the biological mother (n=14), and a case and/or control food frequency questionnaire (FFQ) contained questionable data (i.e., more than 10 foods were skipped, the mother consumed fewer than two or more than 17 solid foods per day, or the energy estimate was greater than 4,500 kilocalories, n=45). Therefore, the final analytic sample included

282 matched case-control sets of children comprising 205 case-control pairs and 77 case-control triplets.

Data collection

We obtained maternal dietary intake by interview, using a modified version of the Block FFQ.[9–11] The time frame covered was the 12 months before the index pregnancy. We chose this period rather than diet during pregnancy because it represents the probable state of nutritional adequacy at the time of conception and during early pregnancy. The FFQ contained 76 food items and questions on vitamin supplement usage. Food items were selected by identifying the top population contributors of each nutrient among white, African American, and Hispanic populations in the Third National Health and Nutrition Examination Survey (NHANES III) and the Hispanic Health and Nutrition Examination Survey (HHANES).[12–14] Frequency of consumption was reported in nine categories, ranging from "never or less than once per month" to "greater than twice per day." We obtained portion size for each food using three-dimensional abstract models. We selected 76 food items to be representative of a wide range of dietary factors including total calories, macronutrients, fiber, vitamins, minerals, and other dietary factors such as carotenoids and phytoestrogens. In addition, we included cured meats and other foods to address prior hypotheses. The vitamin supplement questions asked about two types of multiple vitamins and nine single vitamins, and obtained information on frequency and duration of vitamin use, as well as usual daily dose for vitamins C and E.

We developed a Spanish version of the FFQ to include culturally appropriate translations of the English version and additional foods important in the diets of the Latina population. To identify these foods, we again examined NHANES III and HHANES,[12–14] and also used information from focus groups of Latinas in the San Francisco Bay area. This process resulted in the addition of seven foods (evaporated/condensed milk, green peppers/chile rellenos, avocados/guacamole, chili peppers, mole/sofrito sauces, corn tortillas, and flour tortillas). These items were added only to the Spanish version of the FFQ. Bilingual interviewers administered the questionnaire.

We used the BlockSys program[11] to calculate dietary nutrients from food by multiplying frequency of consumption of each food by its nutrient content and reported portion size, and then summing over all foods. We estimated nutrients obtained from vitamin supplements by multiplying the frequency of consumption of each type (multiple vitamins and specific single vitamins) times the amount of the nutrient in typical compositions of each type. For vitamins E and C, we obtained the usual daily dose from subjects who took those vitamins. We calculated total nutrient intake as the sum of nutrients from foods and supplements, unless otherwise noted. We calculated frequency of consumption of food groups—vegetables, fruits, dairy foods, beans, protein sources, grains, alcoholic beverages, and a group consisting of fats, oils, sweets, and snacks—by summing the reported frequency for all foods in a food group. Food groups corresponded to the food groups found in the U.S. Department of Agriculture Food Guide Pyramid,[15] and their component foods are listed in the Figure. 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.[16–18] Bunin et al. conducted a validation of retrospective assessment of diet before and during pregnancy, and found correlations of the Willett FFQ with reference data to be similar to those obtained for current diet.[19]

We obtained dietary data on each child from the biological mother or primary caregiver using a self-administered questionnaire completed prior to the in-home interview in phase 1 and after the in-home interview in phase 2.[6] The biological mother provided the information in 95% of cases. The wording of the dietary questions did not differ between the two phases of the study. The questionnaire asked about the child's weaning history and the frequency of consumption of nine foods/food groups (hot dogs/lunch meats, beef/hamburger, vegetables, oranges/bananas, apples/grapes, orange juice, other fruit juice, milk, and soda) and vitamin supplements during the child's first and second years of life. Frequency of consumption was reported in six categories, ranging from "rarely or never" to "three or more times a day." In addition, we assessed whether the child consumed vitamins during the first two years of life. To summarize food consumption during the first two years of life, we created new categories of "rare/no consumption," "occasional consumption," and "regular consumption" based on the original categories.

Statistical analysis

We used the Pearson chi-square test to compare selected characteristics of cases and controls. To assess the association between maternal diet and childhood ALL risk, we constructed conditional logistic regression models. We considered odds ratios (ORs) representing dietary consumption on a continuous scale to be statistically significant if the 95% confidence interval (CI) excluded 1.00. Before running the statistical models, we used

Figure. Foods/food groups represented on the food frequency questionnaire, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002[a]

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[b]
Chili peppers, hot chili sauce[b]

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

Protein sources group (USDA Food Guide Pyramid definition)
Hamburgers, cheeseburgers, beef burritos, tacos
Beef, including roasts, steaks, or beef in stir-fry or sandwiches
Pork, including chops, roasts, or pork 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 beans in chili, 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, or other pasta with tomato sauce
Cheese dishes without tomato sauce, such as macaroni and cheese
Pizza
Fiber cereals such as raisin bran, granola, or shredded wheat
Other cold cereals such as corn flakes or Cheerios®
Cooked cereals such as oatmeal, oat bran, or grits
Bagels, English muffins, hamburger buns
Biscuits, muffins
Bread, including white, French, and whole wheat
Corn bread, corn muffins
Corn tortillas[b]
Flour tortillas[b]

Alcohol group
Beer
Wine, wine coolers
Liquor, mixed drinks

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 such as Carnation®, or nutritional energy drinks such as Sego®, Ensure®, or Boost®
Pizza
Cheese dishes without tomato sauce such as macaroni and cheese
Evaporated or condensed milk[b]

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

Miscellaneous (not in other 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, such as soy burgers
Chicken stew, chicken casserole, or stir-fry
Beef or vegetable stew or pot pie
Vegetable soups
Sauces such as mole and sofrito[b]
Guacamole, avocados[b]

Fats, oils, sweets, snacks group
Margarine
Butter
Salty snacks, such as potato or corn chips, popcorn, and crackers
Salad dressing and mayonnaise
Ice cream
Doughnuts, pastries, cookies, granola bars
Chocolate candy, candy bars
Cream, half-and-half, nondairy creamer
Sugar, honey

[a]Includes 282 case-control sets comprising 205 pairs and 77 triplets

[b]Included on Spanish version of food frequency questionnaire only

USDA = U.S. Department of Agriculture

log transformation for variables as needed to improve normality and reduce skewness. Potential confounding variables considered a priori were birthweight of the index child, whether the child was breastfed (yes or no), maternal age, maternal education (≤high school graduate, some college, or college graduate), and smoking during pregnancy (yes or no). However, we observed no evidence of confounding for these covariates, as the change in OR when adding each of these variables to the main model was not considered substantial (greater than 10%). We included total energy consumption, the proportion of foods consumed as large or extra-large portion size, household income, and maternal exposure to indoor insecticides during pregnancy[20] in the final model because these variables explained a significant proportion of the variability in the outcome and, therefore, allowed for a more sensitive test of the relationship between maternal diet and ALL. We also examined the relationship between maternal diet and ALL risk while controlling for the child's diet early in life (intake of hot dogs/lunch meats, beef/hamburger, vegetables, oranges/bananas, apples/grapes, orange juice, other fruit juice, milk, soda, and vitamin supplements; intake was coded as "rarely/none," "occasional," or "regular").

RESULTS

The mean age at ALL diagnosis was 5.2 years, 58% of case children were aged 2 to 5 years at time of diagnosis, and 53% were male (Table 1). Case and control children were similar with respect to birthweight, breastfeeding, and maternal smoking. In terms of race, the study sample was 87% white, 3% African American, and 10% other. Ethnically, approximately 38% of mothers described themselves as Hispanic. Compared with matched control subjects, case children were born to younger mothers (p=0.06) with fewer years of education (p=0.13), and came from families with lower household incomes (p<0.001).

The relationships between maternal consumption of food groups (times/day) and offspring ALL risk for combined phase 1 and 2 data are shown in Table 2. We noted inverse relationships between maternal consumption and childhood ALL risk for the vegetable (adjusted OR [AOR] = 0.65, 95% CI 0.50, 0.84), fruit and vegetable (AOR=0.64, 95% CI 0.48, 0.85), legume (AOR=0.75, 95% CI 0.59, 0.95), and protein sources food groups (AOR=0.55, 95% CI 0.32, 0.96). Fruit consumption was also inversely associated with ALL, but was borderline statistically significant (AOR=0.81, 95% CI 0.65, 1.00). We did not find consumption of cured meats, grains, and dairy products to be significantly related to disease risk. When we included maternal consumption of the vegetable and protein sources food groups together in the model, consumption of both vegetables (AOR=0.65, 95% CI 0.50, 0.84) and protein sources (AOR=0.57, 95% CI 0.32, 0.99) remained associated with a statistically significant decreased risk of ALL.

We also examined the relationship between maternal intake of either the vegetable or protein sources food group and offspring ALL risk while controlling for each of the childhood diet variables individually. In all models, maternal vegetable intake remained statistically significant (p<0.05), whereas maternal consumption of protein sources remained statistically significant when controlling for children's intake of beef/hamburger, hot dogs/lunch meats, oranges/bananas, apples/grapes, soda, orange juice, and vitamins, and was borderline statistically significant (0.05>p<0.09) when controlling for children's intake of vegetables, fruit juice, and milk. In no case did the childhood diet variables reach significance, although several approached significance (p<0.10 for intake of vegetables, oranges/bananas, and orange juice) (data not shown).

Additionally, we examined the maternal consumption of individual foods and found that six foods were inversely related to offspring risk of ALL: carrots, cantaloupe, oranges, green beans, other beans, and beef (Table 3). Regular use of any dietary supplement was not associated with disease risk (AOR=1.10, 95% CI 0.76, 1.60) (data not shown).

Among the macronutrients (Table 4) and micronutrients (Table 5), maternal consumption was inversely associated with offspring ALL for fiber from fruits and vegetables (AOR=0.52, 95% CI 0.31, 0.88), provitamin A carotenoids (AOR=0.77, 95% CI 0.60, 0.98), alpha-carotene (AOR=0.78, 95% CI 0.65, 0.93), total glutathione (AOR=0.48, 95% CI 0.25, 0.90), and reduced glutathione (AOR=0.49, 95% CI 0.27, 0.90). We found borderline significant inverse associations for maternal consumption of beta-carotene (AOR=0.79, 95% CI 0.62, 1.01) and lutein (AOR=0.82, 95% CI 0.66, 1.01).

The direction of the relationships between offspring ALL and maternal consumption of food groups did not change when we examined only case-control sets for case children aged 2 to 5 years at diagnosis (the peak incidence of childhood ALL) and when we restricted the analysis to 81 income-concordant case-control sets, although the magnitude of the relationships was attenuated somewhat and CIs were wider (data not shown).

The data collected during phases 1 and 2 of the

NCCLS represented replications of the study with independent samples and virtually identical methods. Maternal intake of the vegetable and protein sources food groups, and the dietary factors calcium, vitamin A, provitamin A carotenoids, alpha-carotene, total glutathione, and reduced glutathione were significantly related to offspring disease risk in phase 1 and/or phase 2 (Table 6). Of these variables, only consumption of the vegetable food group was statistically significant in both phase 1 and 2 data.

Table 1. Case and matched-control maternal and child characteristics, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002[a]

Matching variables	*Cases (n=282)* N *(percent)*	*Controls (n=359)* N *(percent)*	P-*value*[b]
Child's age (in years)[c]			0.970
<2	34 (12.1)	41 (11.4)	
2–5	164 (58.2)	214 (59.6)	
6–10	61 (21.6)	72 (20.1)	
>10	23 (8.2)	32 (8.9)	
Mean (SD)	5.2 (3.4)	5.2 (3.4)	
Child's gender			0.640
Female	133 (47.2)	176 (49.0)	
Male	149 (52.8)	183 (51.0)	
Child's ethnicity			0.970
Hispanic	108 (38.3)	138 (38.4)	
Not Hispanic	174 (61.7)	221 (61.6)	
Mother's race			0.990
White	244 (86.5)	312 (86.9)	
Black	9 (3.2)	11 (3.1)	
Other	29 (10.3)	36 (10.0)	
Other variables			
Maternal age (in years) at child's birth			0.056
<20	29 (10.3)	25 (7.0)	
20–24	67 (23.8)	67 (18.7)	
25–29	66 (23.4)	103 (28.7)	
30–34	83 (29.4)	106 (29.5)	
≥35	37 (13.1)	58 (16.2)	
Mean (SD)	28.1 (6.1)	29.1 (6.0)	
Maternal education			0.130
≤High school	116 (41.1)	119 (33.2)	
Some college	84 (29.8)	129 (35.9)	
College graduate	82 (29.1)	111 (30.9)	
Annual household income			<0.001
<$15,000	34 (12.1)	31 (8.6)	
$15,000–$29,999	53 (18.8)	52 (14.5)	
$30,000–$44,999	45 (16.0)	39 (10.9)	
$45,000–$59,999	51 (18.1)	56 (15.6)	
$60,000–$74,999	28 (9.9)	44 (12.3)	
≥$75,000	71 (25.2)	137 (38.2)	
Child was breastfed			0.630
Yes	234 (83.0)	303 (84.4)	
Maternal smoking during pregnancy			0.560
Yes	34 (12.1)	38 (10.6)	

[a]Includes 282 case-control sets comprising 205 pairs and 77 triplets

[b]Pearson Chi-square test, two-sided

[c]Age at diagnosis for cases and age at the corresponding date for controls

SD = standard deviation

Table 2. Associations between frequency of maternal consumption of food groups and risk of ALL among offspring, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002[a]

Food group	*Sample median times/day (25th, 75th percentile)*	*AOR (95% CI)[b]*
Vegetables[c]	0.6 (0.4, 1.0)	0.65 (0.50, 0.84)
Fruit[d]	0.6 (0.3, 1.0)	0.81 (0.65, 1.00)
Fruit and vegetables	1.3 (0.8, 2.0)	0.64 (0.48, 0.85)
Grain products	2.6 (2.0, 3.3)	1.20 (0.70, 2.05)
Dairy products	2.1 (1.3, 3.0)	1.06 (0.83, 1.35)
Legumes	0.5 (0.3, 0.8)	0.75 (0.59, 0.95)
Protein sources	1.8 (1.3, 2.5)	0.55 (0.32, 0.96)
Cured meat	0.3 (0.1, 0.5)	0.91 (0.78, 1.05)

[a]Includes 282 case-control sets comprising 205 pairs and 77 triplets

[b]Separate models for each food group as a continuous variable with odds ratios and 95% CIs calculated using log-transformed values of consumption; adjusted for total energy intake, household income, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra-large portion size

[c]Garden vegetables only (excludes salad, potatoes, soup, and stew)

[d]Fruit only (excludes fruit juice)

ALL = acute lymphoblastic leukemia

AOR = adjusted odds ratio

CI = confidence interval

DISCUSSION

In the combined phase 1 and 2 data from the NCCLS, the largest case-control study to date on maternal diet and childhood ALL, we found that intake of the vegetable, fruit, legume, and protein sources food groups in the 12 months before the index pregnancy (and by inference during early pregnancy) was inversely associated with offspring disease risk when adjusted for household income, maternal total energy intake, proportion of foods reported as large or extra-large portion size, and maternal exposure to indoor insecticides during pregnancy. The inverse relationships were strongest for intake of the protein sources and vegetable food groups, suggesting that two distinct maternal dietary patterns are independently and inversely associated with offspring ALL risk.

Maternal vegetable and protein sources intake remained significant and borderline statistically significant, respectively, after further adjustment for the child's diet early in life. In no case did early childhood intake of foods/food groups or vitamin supplements reach significance, although intake of vegetables, oranges/bananas, and orange juice approached statistical significance. Thus, childhood diet may contribute to a reduced risk of ALL as previously reported,[6] but the stronger effect appears to be due to maternal diet.

When examining the diet-disease relationship in the combined data at the level of individual foods, maternal consumption of foods in the fruit and vegetable food groups (i.e., carrots, cantaloupe, and oranges) and the protein sources food group (i.e., green beans, beans, and beef) was inversely associated with offspring ALL risk. At the nutrient level, consumption of provitamin A carotenoids (found in fruits and vegetables) and reduced glutathione (found in protein-containing foods) was inversely related to ALL risk. The study findings may have etiologic relevance in light of evidence that the initiating genetic event in the development of leukemia frequently occurs *in utero*.[4] Fetal exposure to bioactive compounds in vegetables, fruit, and protein foods such as vitamins and minerals, fiber, peptides and amino acids, and other factors may contribute to the ability of these foods to reduce cancer risk.[21–27]

Using virtually identical data collection methods and independent samples from phases 1 and 2 of the NCCLS to examine the reproducibility of our findings, we found that maternal intake of the vegetables food group and its related component, provitamin A carotenoids, was statistically or borderline-statistically associated with decreased offspring ALL risk in both phases of the study. Thus, the inverse diet-disease relationship appears to be strongest for maternal consumption of the vegetable food group.

Our results are generally in agreement with those

Table 3. Associations between maternal consumption of individual foods and risk of ALL among offspring, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002[a]

Individual foods (times/day)	*AOR (95% CI)[b]*
Oranges	0.87 (0.77, 0.99)
Cantaloupe	0.87 (0.76, 0.98)
Green beans	0.85 (0.74, 0.98)
Beans	0.86 (0.74, 0.99)
Carrots	0.82 (0.71, 0.96)
Beef	0.82 (0.69, 0.98)
Fiber cereals	1.12 (1.07, 1.26)

[a]Includes 282 case-control sets comprising 205 pairs and 77 triplets

[b]Separate models for each food group as a continuous variable with odds ratios and 95% CIs calculated using log-transformed values of consumption; adjusted for total energy intake, household income, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra-large portion size

ALL = acute lymphoblastic leukemia

AOR = adjusted odds ratio

CI = confidence interval

of a recently published case-control study of maternal diet and offspring ALL in Greece involving 131 case-control sets.[28] In this study, investigators reported that maternal consumption of the vegetable and fruit food groups was inversely associated with risk of childhood ALL, which is generally consistent with our findings from combined phase 1 and 2 data. While consumption of fish and seafood as a food group was also reportedly associated with reduced risk of disease, consumption of meats and meat products was related to a moderate increase in disease risk,[28] in contrast to our findings.

We observed no evidence of increased offspring ALL risk associated with maternal consumption of cured meats as a food group or individual cured meats, which is consistent with previous reports.[29,30] We also found no evidence of significant risk reduction associated with maternal prepregnancy use of dietary supplements. This is in contrast to previous reports where vitamins A and D from cod liver oil[31] and maternal use of folic acid supplements with or without iron[32] have been reported to be associated with reduced risk of childhood ALL.

Strengths of our study included the use of population-based birth certificate controls that have been shown to be representative of the source population.[8] Matching on race and Hispanic ethnicity reduced some of the biases that can be a problem in other recruitment designs. We obtained the maternal dietary data using a previously validated FFQ, and we designed the extensive food list to assess a wide range of food groups, foods, and nutrients, thus enabling us to control for total energy intake. The child's diet questionnaire, although not validated, was composed of foods that covered a broad spectrum of a typical young child's diet such that we were able to examine its impact on the potential association between maternal diet and

Table 4. Associations between maternal consumption of macronutrients and risk of ALL among offspring, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002[a]

Macronutrient (unit)	*Daily intake estimate: median (25th, 75th percentile)*	*AOR (95% CI)[b]*
Energy (kcal)	1,990 (1,518, 2,582)	0.78 (0.35, 1.74)
Protein (g)	75 (57, 101)	1.18 (0.35, 4.06)
Energy from protein (percent)	15.6 (13.7, 17.5)	1.01 (0.93, 1.09
Total fat (g)	87.7 (65.6, 115.6)	0.62 (0.16, 2.48)
Energy from fat (percent)	40.5 (35.4, 44.9)	0.98 (0.95, 1.02)
Saturated fat (g)	27.5 (20.3, 38.0)	1.32 (0.44, 3.99)
Monounsaturated fat (g)	32.1 (23.7, 43.2)	0.34 (0.09, 1.22)
Polyunsaturated fat (g)	19.0 (13.6, 24.9)	0.78 (0.37, 1.68)
Cholesterol (mg)	254 (177, 349)	1.06 (0.51, 2.23)
Omega-3 fatty acids (mg)	1.61 (1.19, 2.08)	1.15 (0.50, 2.65)
Carbohydrate (g)	224 (169, 300)	1.69 (0.36, 8.01)
Energy from carbohydrates (percent)	45.1 (40.8, 50.2)	1.01 (0.98, 1.05)
Glycemic Index	55.9 (50.6, 59.4)	3.18 (0.51, 19.81)
Glycemic load	113 (83, 154)	2.43 (0.75, 7.87)
Energy from sweets (percent)	8.00 (4.09, 14.5)	0.99 (0.96, 1.02)
Energy from alcoholic beverages (percent)	0.00 (0.00, 0.00)	1.06 (0.92, 1.22)
Dietary fiber, total (g)	15.6 (11.2, 21.2)	0.49 (0.23, 1.04)
Fiber from beans (g)	2.08 (0.87, 4.37)	0.91 (0.73, 1.13)
Fiber from fruits/vegetables (g)	6.18 (0.87, 8.76)	0.52 (0.31, 0.88)
Fiber from grains (g)	5.79 (3.84, 8.58)	0.99 (0.60, 1.63)

[a]Includes 282 case-control sets comprising 205 pairs and 77 triplets

[b]Separate models for each nutrient as a continuous variable with odds ratios and 95% CIs calculated using log-transformed values of consumption; adjusted for total energy intake, household income, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra-large portion size

ALL = acute lymphoblastic leukemia

AOR = adjusted odds ratio

CI = confidence interval

kcal = kilocalorie

g = gram

mg = milligram

Table 5. Associations between maternal consumption of micronutrients and risk of ALL among offspring, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002[a]

Micronutrient (unit)	*Daily intake estimate: median (25th, 75th percentile)*	*AOR (95% CI)[b]*
Vitamins		
Vitamin A (RE)[c]	1,204 (842, 1,789)	0.82 (0.62, 1.08)
Retinol (mcg)	470 (307, 684)	1.17 (0.87, 1.58)
Folate (dietary folate equivalents)[c]	640 (437, 963)	1.02 (0.71, 1.47)
Thiamin (mg)[c]	1.63 (1.21, 2.14)	1.18 (0.73, 1.89)
Riboflavin (mg)[c]	1.93 (1.41, 2.57)	1.29 (0.83, 1.98)
Niacin (mg)[c]	19.8 (14.3, 25.7)	1.05 (0.67, 1.64)
Vitamin B6 (mg)[c]	1.85 (1.36, 2.50)	1.12 (0.73, 1.72)
Vitamin B12 (mcg)[c]	5.34 (3.35, 8.66)	1.10 (0.82, 1.48)
Pantothenic acid (mg)[c]	4.47 (3.37, 5.91)	1.31 (0.62, 2.77)
Vitamin C (mg)[c]	123 (84, 185)	0.96 (0.74, 1.25)
Vitamin D (mg)[c]	185 (114, 282)	1.13 (0.93, 1.36)
Vitamin E (aTE)[c]	10.00 (7.68, 12.90)	0.88 (0.70, 1.10)
Gamma-tocopherol (mg)	20.5 (13.6, 29.3)	0.81 (0.54, 1.20)
Minerals		
Calcium (mg)[c]	844 (612, 1,208)	1.36 (0.91, 2.03)
Zinc (mg)[c]	10.40 (7.49, 14.00)	1.09 (0.78, 1.53)
Iron (mg)[c]	14.2 (10.2, 18.7)	1.05 (0.77, 1.44)
Magnesium (mg)[c]	272 (203, 361)	1.21 (0.63, 2.34)
Phosphorus (mg)	1,244 (911, 1,649)	1.65 (0.69, 3.91)
Sodium (mg)	2,424 (1,888, 3,159)	0.86 (0.29, 2.56)
Potassium (mg)	2,936 (2,249, 3,950)	1.08 (0.47, 2.50)
Selenium (mcg)[c]	96.3 (74.0, 127.0)	0.68 (0.32, 1.44)
Copper (mg)	1.06 (0.78, 1.38)	0.72 (0.32, 1.59)
Manganese (mcg)	2.83 (1.99, 3.96)	1.00 (0.66, 1.50)
Other dietary factors		
Provitamin A carotenoids (mcg)	3,930 (2,434, 6,431)	0.77 (0.60, 0.98)
Alpha-carotene (mcg)	572 (324, 1,111)	0.78 (0.65, 0.93)
Beta-carotene (mcg)[c]	2,553 (1,549, 4,193)	0.79 (0.62, 1.01)
Cryptoxanthin (mcg)	115.0 (52.6, 223.0)	0.97 (0.85, 1.09)
Lutein (mcg)	1,023 (570, 1,773)	0.82 (0.66, 1.01)
Lycopene (mcg)	4,797 (2,415, 8,420)	0.91 (0.76, 1.09)
Daidzein (mcg) (3 categories)	0.00 (0.00, 0.00)	1.19 (0.84, 1.69)
Genistein (mcg) (3 categories)	0.00 (0.00, 0.00)	1.17 (0.82, 1.67)
Glutathione, total (mg)	47.1 (34.0, 64.7)	0.48 (0.25, 0.90)
Glutathione, reduced (mg)	30.3 (21.8, 41.5)	0.49 (0.27, 0.90)
Isoflavones (mg)	1.89 (0.95, 3.58)	1.11 (0.92, 1.33)
Quercetin (mg)	5.56 (3.19, 9.67)	0.92 (0.77, 1.11)

[a]Includes 282 case-control sets comprising 205 pairs and 77 triplets

[b]Separate models for each nutrient as a continuous variable with odds ratios and 95% CIs calculated using log-transformed values of consumption; adjusted for total energy intake, household income, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra-large portion size

[c]Nutrient estimates represent the sum of food and supplement sources. Nutrient estimates for variables without a footnote [c] reflect nutrients only from foods.

ALL = acute lymphoblastic leukemia

AOR = adjusted odds ratio

CI = confidence interval

RE = retinol equivalents

mcg = microgram

mg = milligram

aTE = alpha-tocopherol equivalents

Table 6. Maternal food groups and dietary factors significantly associated with ALL among offspring in either phase 1 or phase 2, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002[a]

Dietary factor	*Phase 1 AOR (95% CI)[b]*	*Phase 2 AOR (95% CI)[b]*
Vegetables food group (times/day)	0.53 (0.33, 0.85)	0.60 (0.42, 0.86)
Protein sources food group (times/day)	0.40 (0.18, 0.90)	0.69 (0.34, 1.42)
Calcium (mg)	0.99 (0.48, 2.04)	1.73 (1.01, 2.94)
Vitamin A (RE)	0.58 (0.32, 0.98)	0.87 (0.60, 1.27)
Provitamin A carotenoids (mcg)	0.65 (0.42, 1.01)	0.73 (0.51, 1.03)
Alpha-carotene (mcg)	0.66 (0.49, 0.90)	0.81 (0.62, 1.05)
Glutathione (mg)	0.48 (0.17, 1.32)	0.33 (0.14, 0.79)
Glutathione, reduced (mg)	0.42 (0.16, 1.10)	0.44 (0.20, 0.99)

[a]Includes 138 case-control sets from phase 1 and 144 sets from phase 2

[b]Separate models for each food group or dietary factor as a continuous variable with odds ratios and 95% CIs calculated using log-transformed values of consumption; adjusted for total energy intake, household income, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra-large portion size

ALL = acute lymphoblastic leukemia

AOR = adjusted odds ratio

CI = confidence interval

mg = milligram

RE = retinol equivalents

mcg = microgram

ALL risk. To our knowledge, this type of comprehensive dietary analysis has not been conducted before in the childhood leukemia literature.

In addition, we obtained nondietary data, which allowed us to evaluate and control for other potential confounding variables. We were able to observe the relationships between maternal diet and offspring ALL risk for all cases, as well as in the subgroup of cases where children were aged 2 to 5 years at diagnosis, thereby increasing our confidence that the findings are generalizable to the majority of childhood ALL cases. Furthermore, the consistent findings of an inverse association between maternal vegetable consumption and childhood ALL risk with independent samples from phases 1 and 2 of the NCCLS support the validity of the findings, although robust replication would involve different investigators and methods, and a different population.

Limitations

Several limitations of these data should be considered. Our data collection focused on maternal diet in the 12 months before the index pregnancy and, therefore, may have the greatest implications for maternal nutritional status immediately before and during early pregnancy. Recall bias is a concern in case-control studies, and although no widely known hypotheses exist about the possible role of maternal dietary factors in childhood leukemia that might lead to recall bias, general hypotheses about a "healthy" diet could have led case mothers to underreport their intake of perceived healthy foods such as vegetables and fruits. However, it is difficult to imagine that this would hold true for reported consumption of protein sources. Measurement error is a problem in research requiring self-reports; however, data collection methods did not differ between cases and controls in this study. Thus, misclassification from measurement error would be expected to be nondifferential and would likely, although not always, bias the results toward the null.

The participation rate of controls was modest, and controls tended to have higher incomes and more education than cases; as a result, selection bias must be considered as a factor in interpreting our results. A selection that favored controls with higher income and education might produce an inverse association between disease risk and vegetable consumption, as higher socioeconomic status is associated with higher consumption of fruits and vegetables.[33,34] However, it would be unlikely to result in an inverse association with consumption of protein sources (meats and legumes), which are less frequently consumed among more affluent or well-educated groups.[35] In addition, such a selection bias should also have produced an apparently protective effect of dietary supplements, as the more affluent and well educated do take more vitamin supplements.[36,37] However, we did not find an inverse association with dietary supplement use. Also, to account for differences in socioeconomic status, we controlled for household income, matched

on Hispanic ethnicity, and repeated the analysis in income-concordant pairs, with no material change in our findings. Finally, dietary factors are often correlated with one another. Thus, caution is warranted in directly attributing risk or benefit to any particular food or nutrient.

CONCLUSIONS

Maternal intake of the vegetable, fruit, legume, and protein sources food groups was found to be inversely associated with offspring ALL risk. The associations were strongest for consumption of protein sources and vegetable food groups, and their relationships with disease risk were independent of one another and the child's diet early in life. Although causality cannot be inferred from this study, the data suggest that it may be prudent for women to consume a diet rich in vegetables and adequate in protein prior to and during pregnancy as a possible means of reducing the risk of ALL in their offspring.

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