Maternal Diet and Acute Lymphoblastic Leukemia in Young Children

Eleni Petridou,[1,2] Evangelos Ntouvelis,[1] Nick Dessypris,[1] Agapios Terzidis,[1] Dimitrios Trichopoulos,[1,2] and the Childhood Hematology-Oncology Group

[1]Department of Hygiene and Epidemiology, Athens University Medical School, Athens, Greece and
[2]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

Abstract

Because leukemia clone-specific chromosomal abnormalities are present at birth in children who later develop leukemia, it has been hypothesized that maternal factors, including nutrition during pregnancy, might affect the risk of acute lymphoblastic leukemia (ALL) among young children. We have evaluated this hypothesis in a nationwide case-control study of ALL among children ages 12 to 59 months in Greece. Children (n = 131) with ALL were gender and age matched to control children (n = 131) hospitalized for minor conditions between 1999 and 2003. The mothers of the children were interviewed in person by trained interviewers who used an extensive food frequency questionnaire addressing diet during the index pregnancy. The analysis was done by modeling the data through conditional logistic regression, also controlling for total energy intake and possible confounding factors. Odds ratios (OR) and 95% confidence intervals (95% CI) were expressed per quintile increase of maternal intake during pregnancy of the specified food group. The risk of ALL in the offspring was lower with increased maternal intake of fruits (OR, 0.72; 95% CI, 0.57-0.91), vegetables (OR, 0.76; 95% CI, 0.60-0.95), and fish and seafood (OR, 0.72; 95% CI, 0.59-0.89) and higher with increased maternal intake of sugars and syrups (OR, 1.32; 95% CI, 1.05-1.67) and meat and meat products (OR, 1.25; 95% CI, 1.00-1.57). Children of women who tend to consume during their pregnancies what is currently considered to be a healthy diet maybe at lower risk of ALL. (Cancer Epidemiol Biomarkers Prev 2005;14(8):1935–9)

Introduction

With the exception of ionizing radiation (1) and some rare genetic abnormalities (2, 3), causes of childhood acute lymphoblastic leukemia (ALL) have not been identified (4, 5). Two lines of evidence point to the intrauterine environments as playing a major etiologic role: (*a*) leukemia clone-specific chromosomal translocations are present at birth in children who have later developed leukemia (6, 7) and (*b*) birth weight has been frequently found to be associated with risk of ALL (8-14), particularly among children ages <5 years (15-17), although null results have also been reported (18-20). The first line of evidence tends to incriminate prenatal exposures. The second line of evidence points to quantitative or qualitative aspects of maternal diet during pregnancy 21, 22), although hormonal factors may also be important (23). Accordingly, children ages <5 years with ALL represent an appropriate group for the documentation of the maternal diet-childhood ALL association, if such an association actually exists.

We have undertaken a nationwide study of ALL among children ages <5 years in Greece with focus on maternal diet during the index pregnancy. We have not included cases of infant leukemia, because the majority of them has a specific genetic abnormality in the *11q23* chromosome band involving the *MLL* gene (24, 25).

Subjects and Methods

A nationwide network comprising all six Childhood Hematology-Oncology Departments has been established in the mid-1980s and has conducted several epidemiologic investigations concerning childhood hematologic malignancies (26-28). For the present study, all 171 cases of ALL ages 1 to 4 years (12-59 completed months of age) first diagnosed anywhere in Greece from January 1999 to June 2003 were eligible. Five ALL cases diagnosed among infants during the study period were not included based on the protocol. For 21 cases diagnosed in one of the two departments located in Thessaloniki, data were not available, but their exclusion is unlikely to have introduced selection bias because it was based on administrative reasons. For another 9 cases from the remaining five departments, consent for inclusion in the study was not obtained. Thus, 141 cases were eligible from the two Departments of ''Aghia Sophia'' General Children's hospital and the single Department of Children's Hospital of Athens ''Kyriakou,'' from the Department of the American Hellenic Educational Progressive Association Hospital in Thessaloniki, and from the Department of the University Hospital in Heraklion, Crete. The initially enrolled hospitals are all five children's hospitals in Greece, and although children are also admitted in pediatric wards of general hospitals, the bulk of childhood morbidity is dealt in the children's hospitals.

An attempt was made to match each ALL case with one control of the same gender and similar age (±6 months), concurrently hospitalized in the same institution for minor conditions and without a history of cancer or overt nutritional or metabolic disorder. For 10 ALL cases, the

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Requests for reprints: Eleni Petridou, Ass. Professor of Preventive Medicine and Epidemiology, Department of Hygiene and Epidemiology, Athens University Medical School, 75 Mikras Asias str., Goudi, Athens 115-27, Greece. Phone: 30-210-7462187; Fax: 30-210-7462105. E-mail: epetrid@med.uoa.gr

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mother was not available or no suitable control child was found. In 7 instances, control children could not be enrolled because of inaccessibility of their mothers, but they were appropriately substituted. Thus, the study was eventually based on 131 individually matched pairs of ALL cases and control children. The admission diagnoses of the control children were mild respiratory conditions (29 controls), viral infections (33 controls), allergy (16 controls), gastrointestinal or genitourinary conditions (18 controls), nervous system conditions (12 controls), and injuries (23 controls). The Ethics Committee of the University of Athens Medical School approved the study protocol and all procedures were in accordance with the Helsinki declaration for human rights.

The mothers of the 131 case-control pairs who have consented to participate were interviewed in person by trained interviewers, the same for each case-control pair. Interviews took place in the respective health care settings. The questionnaire used covered sociodemographic variables and an extensive section assessing maternal dietary intakes, including typical portion sizes, during the index pregnancy. Specifically, the mothers were asked to indicate the average frequency of consumption during pregnancy, per month, per week, or per day, of the indicated portion sizes of 157 food or beverage items. The dietary questionnaire has been previously validated among adult men and nonpregnant women (29).

For the analysis, the frequency of intake of each food item was translated into average daily quantity of intake (in g/d) and the food items were combined into nine groups in a variation of the scheme recommended by Davidson and Passmore (30) and regularly used in nutritional epidemiologic studies in Greece (31, 32). The food groups were cereals and starchy roots, sugars and syrups, pulses and nuts, vegetables, fruits, meat and meat products, fish and seafood, milk and dairy products, and butter and margarine. Some cooked meals were allocated into more than one food groups (e.g., ''pastitsio'' was allocated 50% into cereals and 50% into meats). Total energy intake was also calculated by multiplying the energy content of the typical portion of each food item by the frequency the food item was consumed and adding the products over all food items (33). Intakes of energy (in kcal/d) and intakes of each of the nine food groups (in g/d) were then distinguished into quintiles based on the respective distributions of the cases and controls combined, apart from intake of butter and margarine that could only be distributed in tertiles.

For the statistical analysis, cases and controls were distributed by marginal quintiles. A χ statistic (the square root of χ^2 with 1 *df*) was used to assess the direction and the statistical significance of the association between maternal consumption of foods of a particular group and ALL risk in the offspring, without adjustment for covariates. Adjustment for the matching variables, birth weight (continuously in 500 g increments), as well as maternal age (continuously in 3-year increments), years of schooling (in three categories, ordered), occupation (yes/no), energy intake (continuously, in increments of 1 SD among controls), and tobacco smoking during pregnancy (yes/no), was accomplished by modeling the data through conditional logistic regression. Covariates were chosen as possible predictors of either maternal dietary intakes or disease risk and thus as conceivable confounders of the association maternal dietary intakes and childhood ALL in the present data set. To this core model, intake of each of the nine food groups was alternatively added (in quintiles, ordinally, except for butter and margarine). The SAS statistical package was used in all instances (34).

Results

Of the 131 cases of ALL, 75 were boys and 56 were girls. Within the age group under investigation, there were more cases ages 2 to 3 years than younger and older ones. There is evidence that maternal smoking during pregnancy increases the risk for ALL among children ages 1 to 4 years and suggestive evidence for a positive association between maternal age at birth and risk of this disease. In contrast, in this data set, birth weight is not related to ALL risk (Table 1). These data, however, are not mutually adjusted and the indicated associations are explored further on.

In Table 2, cases and controls are compared with respect to consumption of each of the nine food groups as well as total energy intake. The food group associations in this table are not adjusted for energy intake, maternal age at birth, or birth weight, nor do they accommodate the matched design of the study. Nevertheless, there is evidence in the data that increased maternal consumption of sugars and syrups as well as of meat and meat products increases the risk of ALL in the offspring, whereas increased maternal consumption of fruits and perhaps vegetables reduces the risk.

The data in Table 3 indicate that after mutual adjustment there are significant positive associations of ALL at ages 1 to 4 years with maternal age at birth as well as with tobacco smoking and energy intake during pregnancy. In this data set, maternal years of schooling, as an indicator of socioeconomic status, maternal occupation, and birth weight, are not associated with ALL risk. Introduction, one at a time, of the nine food groups under study in ordered quintiles (tertiles for butter and margarine) in the model presented in Table 3 reveals several significant associations with ALL risk: inverse for fruits, vegetables, and fish and seafood and positive for

Table 1. Distribution of 131 cases of ALL ages 1 to 4 years and 131 age- and gender-matched controls by gender, age, maternal age at birth, birth weight, maternal smoking during pregnancy, maternal years of schooling, and maternal occupation

Variables	Cases, *n* (%)	Controls, *n* (%)	*P*
Gender			
Male	75 (57.3)	75 (57.3)	Matched variable
Female	56 (42.7)	56 (42.7)	
Age (y)			
1	26 (19.8)	22 (16.8)	Matched variable
2	42 (32.1)	41 (31.3)	
3	39 (29.8)	44 (33.6)	
4	24 (18.3)	24 (18.3)	
Maternal age at the time of delivery (y)			
<23	20 (15.2)	24 (18.3)	0.08*
23-25	23 (17.6)	24 (18.3)	
26-28	18 (13.8)	25 (19.1)	
29-31	21 (16.0)	27 (20.6)	
32-34	27 (20.6)	17 (13.0)	
≥35	22 (16.8)	14 (10.7)	
Birth weight (g)			
<3,000	33 (25.2)	22 (16.8)	0.48*
3,000-3,499	48 (36.6)	58 (44.3)	
3,500-3,999	39 (29.8)	42 (32.0)	
≥4,000	11 (8.4)	9 (6.9)	
Maternal smoking during pregnancy			
No	101 (77.1)	115 (87.8)	0.02
Yes	30 (22.9)	16 (12.2)	
Maternal years of schooling			
<12	41 (31.3)	32 (24.4)	0.49*
12	58 (44.3)	68 (51.9)	
≥13	32 (24.4)	31 (21.7)	
Mother employed			
No	61 (46.6)	59 (45.0)	0.80
Yes	70 (53.4)	72 (55.0)	

*P from χ^2 for trend (1 *df*).

Table 2. Distribution of 131 cases of ALL ages 1 to 4 years and 131 age- and gender-matched controls by maternal intake of energy and specified food groups

Variable	Quintiles					*P* for trend
	1st	2nd	3rd	4th	5th	
Cereals and starchy roots						
Cases	21	27	27	27	29	0.13
Controls	33	25	24	26	23	
Quintile median (g/d)	52	74	95	113	164	
Sugars and syrups						
Cases	21	19	29	29	33	0.004
Controls	31	34	23	23	20	
Quintile median (g/d)	10	25	44	79	152	
Pulses and nuts						
Cases	24	26	22	31	28	0.38
Controls	16	38	33	24	20	
Quintile median (g/d)	4	7	10	13	17	
Vegetables						
Cases	32	24	29	23	23	0.09
Controls	19	30	24	28	30	
Quintile median (g/d)	50	76	100	128	163	
Fruits						
Cases	28	34	24	23	22	0.04
Controls	24	18	30	29	30	
Quintile median (g/d)	51	84	122	157	228	
Meat and meat products						
Cases	23	28	17	29	34	0.01
Controls	30	30	31	24	16	
Quintile median (g/d)	25	33	39	46	61	
Fish and seafood						
Cases	36	28	16	23	28	0.09
Controls	20	25	24	41	21	
Quintile median (g/d)	3	6	7	9	14	
Milk and dairy products						
Cases	31	24	25	20	31	0.49
Controls	21	27	25	35	23	
Quintile median (g/d)	39	60	76	93	127	
Butter/margarine						
Cases	42	45	44			0.07
Controls	51	50	30			
Tertile median (g/d)	0	6	21			
Daily energy intake						
Cases	26	24	25	23	33	0.28
Controls	26	29	27	29	20	
Quintile median (kcal/d)	1,415	1,689	1,898	2,164	2,667	

Table 3. Conditional logistic regression–derived, mutually adjusted ORs and 95% CIs for ALL at ages 1 to 4 years by core model variables

Variable	Category or increment	OR (95% CI)	*P*
Maternal age at the time of delivery	3 y more	1.20 (1.01-1.42)	0.04
Birth weight	500 g more	0.91 (0.68-1.22)	0.55
Maternal smoking during pregnancy	No	Baseline	
	Yes	2.84 (1.29-6.22)	0.01
Maternal years of schooling	One category more	0.99 (0.68-1.44)	0.96
Mother employed	No	Baseline	
	Yes	1.03 (0.58-1.82)	0.93
Maternal daily total energy intake during pregnancy	1 SD among controls	1.31 (1.04-1.66)	0.02

sugars and syrups and meat and meat products (Table 4). Controlling for maternal occupation in specific job categories (professionals, white color nonprofessional workers, manual workers, and no occupation besides homework) and for tobacco smoking according to whether mothers were actually smoking during the index pregnancy had no effect on the odds ratio (OR) estimates given in Table 4.

We have also run several models with mutual adjustment of two or more of the food groups indicated in Table 4. In general, the direction of the associations did not change, but their strength was reduced (ORs tended toward the null) and the corresponding 95% confidence intervals (95% CI) increased because of the underlying intercorrelations and the overdetermination of the models (data not shown).

Discussion

In a nationwide case-control study in Greece on ALL among children ages 12 to 59 months, we have found evidence that maternal consumption during pregnancy of increased quantities of vegetables, fruits, and fish and seafood is associated with reduced risk of the disease in the offspring, whereas increased maternal consumption of meat and meat products and sugars and syrups is associated with increased risk of ALL among their young children. A marginal inverse association was also noted with respect to maternal consumption of milk and dairy products. In essence, our results indicate that a diet generally considered as ''healthy'' (35) for adults may, if consumed during pregnancy, also reduce the risk of ALL among offspring.

Strengths of the present study are its nationwide coverage; its satisfactory size, considering that it refers to a relatively rare disease in a relatively small country; the smooth cooperation on the part of the children's mothers in the hospital environment; the use of a dietary questionnaire that has been validated, although not among pregnant women; the high comparability between cases and controls in the interviewing conditions; and control, in the analysis, for all available variables that could have confounding potential. The study has also several weaknesses, including those inherent in case-control investigations. An additional weakness was enrollment of hospital, rather than general population, controls. In Greece, few women in the general population are willing to discuss issues concerning the health of their children with essentially unknown persons, not withstanding their credentials. Hospital controls, however, were enrolled among those attending the large pediatric hospitals, which are treating the bulk of childhood morbidity in Greece and in which the participating pediatric hematology/oncology units were situated (36). Care was also taken that hospital controls had diagnoses that have not been linked to maternal, as contrasted to own diet. We have no information on actual income (the question is considered too sensitive), and we could not ascertain how well the diet of control women approximates the diet of pregnant women in

Table 4. Conditional logistic regression–derived ORs and 95% CIs for ALL at ages 1 to 4 years by maternal intake of specified food groups

Variable	Increment	OR (95% CI)	*P*
Cereals and starchy roots	One quintile more	1.23 (0.94-1.60)	0.13
Sugars and syrups	One quintile more	1.32 (1.05-1.67)	0.02
Pulses and nuts	One quintile more	0.96 (0.77-1.20)	0.73
Vegetables	One quintile more	0.76 (0.60-0.95)	0.01
Fruits	One quintile more	0.72 (0.57-0.91)	0.007
Meat and meat products	One quintile more	1.25 (1.00-1.57)	0.05
Fish and seafood	One quintile more	0.72 (0.59-0.89)	0.003
Milk and dairy products	One quintile more	0.82 (0.66-1.02)	0.08
Butter/margarine	One tertile more	1.41 (0.97-2.06)	0.07

NOTE: Controlling for matching variables, maternal age at birth, birth weight, maternal smoking during pregnancy, maternal years of schooling, maternal occupation, and maternal daily energy intake during pregnancy but not mutually among food groups.

the general Greek population (there are no relevant studies that have used the food frequency questionnaire employed in the present investigation). It has not been possible to inquire about intake of illicit drugs and we have had considerable difficulties in ascertaining olive oil intake, because this food is consumed almost universally. Lastly, misclassification of dietary exposures is certainly present, but it is likely to be nondifferential and thus unlikely to generate false associations or exaggerate genuine ones.

The Greek diet most closely approximates the traditional Mediterranean diet. This diet is characterized by high intake of vegetables, legumes, fruit, and cereals; a high intake of olive oil; a low intake of saturated lipids; a moderately high intake of fish; a low to moderate intake of dairy products (mostly in the form of cheese or yogurt); and a low, but rapidly increasing during the last few decades, intake of meat and meat products (37). In this investigation, we have focused on food groups rather than nutrients, in line with the strategy adopted in the early studies investigating the relation of diet to adult onset chronic diseases, including cancer (38).

In our study, maternal age at birth was positively associated with ALL risk in the offspring, in line with reports from several recent larger investigations (39-41). We have not been able to document in this data set the association of birth weight and childhood ALL (14). It is not unusual, however, to fail to document a relatively weak association in a study with moderate statistical power, as it has also happened with the birth weight and ALL association in other investigations (18-20). The positive association in our data between maternal smoking and ALL in the offspring has occasionally been reported in other investigations (42) but has not been documented in several others (43). The higher total energy intake during pregnancy of the mothers of ALL cases in comparison with those of control children may reflect relative overreporting, which was controlled for in the analysis, or may reflect a genuine phenomenon that needs to be evaluated in future investigations.

Few investigations have examined maternal diet during or immediately before pregnancy in relation to ALL in the offspring. The results of these studies as well as those of our investigation are remarkably consistent in spite of differences in methodologic and sample characteristics. Blot et al. (44) reviewed in 1999, among other issues, the limited at the time evidence concerning consumption during pregnancy of cured meat, a source of potentially carcinogenic *N*-nitroso compound, and childhood malignancies, including ALL. They have noted that some of the studies, despite using limited dietary questionnaires, were indicative of a positive association. Thompson et al. (45) reported that offspring of women who during their pregnancies received supplements with folate (naturally found in several leafy vegetables) had lower risk of ALL. Additionally, Jensen et al. (46) have found that increased maternal intake immediately before the index pregnancy (and inferentially, during that pregnancy) of vegetables and fruits was associated with decreased risk of ALL.

In conclusion, we have found evidence that young children of women who during their index pregnancy tend to consume what is currently considered to be a ''healthy'' diet, which is a diet high in vegetables, fruits, fish, and seafood and low in meat and meat products, sugars, and syrups, have a lower risk of ALL. These results are consistent, but more striking, with those previously reported from other investigators. If confirmed, our findings would indicate that the incidence of ALL among young children could be reduced by maternal adherence during pregnancy to the generally accepted principles concerning a healthy diet throughout life.

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