Maternal Diet and Infant Leukemia: The DNA Topoisomerase II Inhibitor Hypothesis: A Report from the Children's Oncology Group

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Abstract

Background: **The MLL 11q23 translocation arises *in utero* and is present in 75% of infant leukemias. That MLL+ acute myeloid leukemia (AML) can arise following chemotherapy with DNA topoisomerase II (DNAt2) inhibitors suggests that these substances, which also occur naturally in foods, may contribute toward infant leukemia. We hypothesized that maternal consumption of dietary DNAt2 inhibitors during pregnancy would increase the risk of infant leukemia, particularly AML(MLL+).**
Methods: **This Children's Oncology Group case-control study consisted of 240 incident cases of infant acute leukemia [AML and acute lymphoblastic leukemia (ALL)] diagnosed during 1996 to 2002 and 255 random digit dialed controls. Maternal diet during pregnancy was determined through a food frequency questionnaire. An index of specific foods identified *a priori* to contain DNAt2 inhibitors as well as vegetables and fruits were created and analyzed using unconditional logistic regression.**

Results: **There was little evidence of an association between the specific DNAt2 index and leukemia overall and by subtype. An exception was AML(MLL+); odds ratios (95% confidence intervals) comparing the second to fourth quartiles to the first were 1.9 (0.5-7.0), 2.1 (0.6-7.7), and 3.2 (0.9-11.9), respectively (*P* for trend = 0.10). For the vegetable and fruit index, there were significant or near-significant inverse linear trends for all leukemias combined, ALL(MLL+), and AML(MLL−).**
Conclusion: **Overall, maternal consumption of fresh vegetables and fruits during pregnancy was associated with a decreased risk of infant leukemia, particularly MLL+. However, for AML(MLL+) cases, maternal consumption of specific DNAt2 inhibitors seemed to increase risk. Although based on small numbers, these data provide some support for distinct etiologic pathways in infant leukemia.** (Cancer Epidemiol Biomarkers Prev 2005;14(3):651–5)

Introduction

Leukemia in infants ages <1 year is rare but devastating. The annual incidence is 35.9 cases per 1 million children; acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) make up ~50% and 30% of infant leukemias, respectively, with the rest being chronic or unspecified (1). The 5-year survival rate for infants is only ~42% compared with 82% for children ages between 1 and 4 years, with the difference being much more dramatic for ALL (1).

About 75% of infants with leukemia have cells that display a rearrangement involving the *MLL* gene at chromosome band 11q23 (2, 3). The *MLL* gene, which shows a high degree of homology to the fruit fly homeobox gene, *trithorax*, seems to play an important role in normal hematopoiesis [reviewed by Ernst et al. (4)]. *MLL* gene rearrangements have been detected in the neonatal bloodspots of infants who later developed leukemia (5). Identical twins have high (~100%) concordance

for infant leukemia and the leukemia cells of some twin pairs have displayed *MLL* gene rearrangements with identical breakpoints [reviewed by Greaves et al. (6)]. Together, this evidence shows that the *MLL* gene rearrangement arises *in utero* (and, in identical twins, migrates from one twin to the other).

In light of those data, etiologic investigations have focused recently on exposure to potentially leukemogenic substances during gestation. Of particular interest are substances that alter the function of the DNA topoisomerase II (DNAt2) enzyme, which relaxes supercoiled DNA by transiently cleaving and religating both strands of the double helix (7) and is highly expressed in developing fetuses (8). Epipodophyllotoxins have been used to treat a variety of cancers (9) because they disrupt the normal cleavage-religation reaction of DNAt2, which has the overall effect of enhancing cleavage, and the resultant DNA double-strand breaks lead to apoptosis (7). Risk of secondary AML with the *MLL* gene rearrangement is significantly increased among patients treated for cancer with epipodophyllotoxins (10, 11); secondary ALL can also occur but to a much lesser extent (12). Thus, we hypothesized a decade ago that exposure of the developing fetus to environmental DNAt2 inhibitors could increase the risk of *de novo* leukemia among infants (13).

The most abundant environmental source of DNAt2 inhibitors is diet. In particular, there are flavonoids, such as quercetin, in some fruits and vegetables; genistein in soy; and catechins in green and black tea, cocoa, and red wine that

inhibit DNAt2 (14-16). Preliminary laboratory (15-17) and epidemiologic (18-20) evidence are consistent with a role for dietary DNAt2 inhibitors in infant leukemia etiology. However, vegetables and fruit contain many other compounds, some of which have known anticancer activity, as appears to be true for vegetables and fruits more generally (21).

We now report on the largest case-control study to date of maternal diet and infant leukemia. Our hypothesis was that high levels of dietary DNAt2 inhibitors would be associated with increased risk of MLL+ 11q23 infant leukemia. Based on the results of our earlier study that found an increased risk only for AML (18) and the observed increased risk for secondary AML(MLL+) following treatment with epipodo-phyllotoxins (10), we further speculated that an association with dietary DNAt2 inhibitors would be more pronounced in this subset of AML(MLL+) cases.

Subjects and Methods

Human Subjects. A case-control study was conducted to investigate potential risk factors for leukemia in the first year of life. The human subject protection committees of the University of Minnesota and each Children's Oncology Group (COG) institution approved all aspects of the study protocol (COG-AE24). COG institutions treat virtually all children in the United States with leukemia diagnosed at age <5 years (22). Eligibility for cases included (*a*) a primary diagnosis of acute leukemia (*International Classification of Diseases, Ninth Edition* codes 9801, 9803, 9821, 9823, 9861, 9863, 9910, and 9913) diagnosed during the first year of life at COG member institutions between January 1, 1996 and August 20, 2002; (*b*) residence in a home with a telephone at the time of diagnosis; (*c*) availability for interview of an English-speaking biological mother; and (*d*) no Down syndrome. Controls were identified by random digit dialing of telephone numbers based on the exchanges of the cases' telephone numbers at the time of diagnosis (23). Eligibility for controls also included items *c* and *d* above. Controls were frequency matched to cases on year of birth.

Data Collection and Format. After giving informed consent, mothers were interviewed by telephone using a structured, computer-assisted questionnaire. Questions included items on demographics, reproductive history, exposures during pregnancy with case or control children (index pregnancy), including diet, and birth characteristics of case or control child (index child). Mothers were also asked for consent to obtain medical records from 2 years before the index pregnancy to 1 week after birth of the index child. A nurse trained in medical record abstraction recorded information on prescription medications and events during the index pregnancy. Detailed reports of leukemia cell cytogenetic and molecular abnormal-ities were also requested for cases.

Diet was the main focus of this analysis. A modified version of the Fred Hutchinson Cancer Research Center's food frequency questionnaire was used to assess the frequency of consumption by mothers of a variety of foods (*n* = 31 items in total)[10] and specific alcoholic beverages (red/white wine/wine coolers, beer, and liquor/mixed drinks) during the index pregnancy. Mothers were asked, separately, the frequency of consumption of beverages before and after they knew they were pregnant with the index child because consumption of

some beverages (e.g., coffee) can often change once a woman learns she is pregnant. We asked about the frequency of consumption of other food items for the entirety of pregnancy. The choices for frequency of consumption of food items were as follows: never, less than once monthly, once to thrice monthly, once to thrice weekly, four to six times weekly, once daily, and more than once daily. For the purpose of analysis, these answers were assigned values of 0, 4.5, 18, 78, 195, 274, and 548, respectively (i.e., the answers were assigned the average number of times they reported eating a particular food item during a typical 40-week pregnancy). For example, a woman who answered that she ate apples between four and six times weekly while pregnant would have eaten five apples weekly on average for 40 weeks for a total of 200 apples. To estimate beverage consumption over the entire pregnancy, we calculated a weighted average giving one-third weight to the frequency of consumption of a beverage before a woman knew she was pregnant and two-third weight to the frequency after (based on the assumption that most women learn of their pregnancies at about the end of first trimester).

An index was created that summarized the frequency of consumption of DNAt2 inhibitor-containing foods: the specific DNAt2 inhibitor index consisted of foods that were identified *a priori* through an extensive literature search (13, 14) to contain DNAt2 inhibitors. These foods were canned or dried legumes, onions, apples, berries, soy products, coffee, black tea, green tea, cocoa, red wine, and caffeinated beverages other than coffee. A vegetable and fruit plus (VF+) index consisting of the sum of the values for frequency of fresh and canned fruits and vegetables, canned or dried legumes, soy (either soy sauce or other soy), coffee, black tea, green tea, cocoa, red wine, and other caffeinated beverages was also created for compar-ison with our previous analysis (18). The indices were categorized into quartiles based on their distributions in cases and controls combined.

We considered several potential confounders in our analysis. Continuous covariates, such as mother's age at birth of index child, birth weight of index child in grams, and number of prior fetal deaths, were evaluated. We categorized the other potential confounders as follows: race/ethnicity (White, Black, Hispanic, other), sex (male, female), morning sickness during index pregnancy (yes, no), family income during index pregnancy (<$30,000, $30,000-75,000, >$75,000), and mother's education at the time of birth of the index child (high school graduate or less, some college or trade school, college degree or greater), smoking during index pregnancy (yes, no), and drinking during index pregnancy (yes, no).

Cases were classified by leukemia type (ALL or AML) and translocation status (MLL+, MLL−, and indeterminate). Translocation status was determined by molecular methods (Southern blot and PCR), conventional cytogenetic analysis, and/or fluorescence *in situ* hybridization. French-American-British morphology also was determined (24, 25). All molecular and cytogenetic reports were independently reviewed by two of the coauthors (N.A.H. and J.H.). We considered a case to be MLL+ if either molecular or cytogenetic methods indicated the rearrangement. Whenever possible, two karyotypes of the abnormal clone were reviewed to confirm cytogenetic data. In those cases, the reviewed karyotype was used to determine 11q23 status. In cases where karyotypes were not available for review, the patient's cytogenetic laboratory report was reviewed. Patients with balanced translocations with 11q23 breakpoints were considered to have a MLL rearrangement. Patients with deletions of 11q were considered MLL− (26). Patients with other recurrent aberrations were classified as MLL−. Unless molecular testing had been done, normal chromosomes were considered indeterminate, as the abnormal clone may have been missed.

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10 Ice cream, butter/margarine, yogurt, cheese, eggs, canned or dried beans and lentils, fish, fresh vegetables other than potatoes, canned or frozen vegetables, fresh fruit, canned or frozen fruit, milk, poultry, red meats, cured meats, soy products excluding soy sauce, soy sauce, pickles, onions, tomatoes, potatoes, apples, berries, nuts, cocoa, caffeinated soft drinks, coffee, decaffeinated coffee, herbal tea, black tea, and green tea.

A total of 149 cases were classified as ALL and 91 as AML. Among ALL cases, 84 were MLL+ (67 by molecular methods), 43 were MLL− (30 by molecular methods), and 22 had indeterminate MLL status. Among the AML cases, 29 were MLL+ (11 by molecular methods), 37 were MLL− (9 by molecular methods), and 25 had indeterminate MLL status.

Statistical Methods. In our descriptive analysis, the t test for two proportions for continuous variables and the χ^2 test for discrete variables were used. Associations between DNAt2 inhibitor indices and infant leukemia were evaluated using unconditional logistic regression (27). SAS PROC LOGISTIC calculated odds ratios (OR) and 95% confidence intervals (95% CI). Each index was analyzed in a separate logistic regression model to avoid the problem of multicollinearity. The indices were analyzed as continuous variables, from which the P for linear trend was derived, and as categorical variables. We adjusted for three demographic covariates—mother's age at birth of index child, household income, and mother's education—as a matter of course and assessed the confounding effect of the other covariates thereafter. We considered a covariate to be a confounder if its addition to the logistic regression model changed the variable estimate of the continuous DNAt2 inhibitor indices by >10% in either direction (28). In addition to the analysis of the entire group of cases, we compared controls with case subgroups defined by leukemia type and MLL status separately and in combination. We assessed confounding separately for each subgroup of cases.

Results

Participation. During the study period, a total of 348 potential cases were identified through 126 COG institutions participating in the study. Maternal interviews were successfully completed for 240 (69%) of those eligible. Reasons for noninterview included maternal refusal (17%), physician refusal (7%), and inability to locate mother (7%).

We randomly selected 25,516 telephone numbers for the study. Among the 11,713 residential telephone numbers identified, 3,638 could not be screened, 7,394 belonged to households with no eligible children, and 253 refused screening; 430 telephone numbers belonged to families who had at least one child eligible for the study. Our random digit dialing screening response rate was therefore 67% (29). We successfully completed a telephone interview with the mother for 255 of 430 potential controls for a random digit dialing field rate of 59% (29). Reasons for nonparticipation among potential controls included 133 (31%) refusal, 35 (8%) telephone number changes resulting in a loss to follow-up, and 5 (1%) who were unable to schedule an interview before completion of the study.

Descriptive Statistics. Table 1 compares selected characteristics of study subjects. Case mothers were not significantly different from control mothers on age at birth of child, education, smoking, drinking during pregnancy, or morning sickness. About 52% of cases were male compared with ~48% of controls, but this difference was not statistically significant. Differences between cases and controls in birth weight and maternal education also were not statistically significant. Cases were dissimilar to controls on race (79.5% of cases were White versus 85.5% of controls; P = 0.003) and household income (14.4% of cases >$75,000/y versus 24.0% of controls; P = 0.03).

DNAt2 Inhibitor Indices. Adjusted ORs for total consumption of specific DNAt2 inhibitor-containing foods are shown in Table 2. Other covariates were not confounders by our criteria in any of the analyses. There was little evidence of an association between the specific DNAt2 inhibitor index and most groups defined by subtype and MLL status. With one exception, the Ps for linear trend ranged from 0.19 to 0.88 and ORs for quartiles of the specific index were not statistically

significant and did not display an obvious pattern. Risk of AML(MLL+), however, increased with increasing values of the specific DNAt2 inhibitor index. Despite a few cases (n = 29), the P for trend was 0.10 and the ORs (95% CIs) comparing the second to fourth quartiles of the index to the first were 1.9 (0.5-7.0), 2.1 (0.6-7.7), and 3.2 (0.9-11.9), respectively. Recognizing that small cell counts can produce unstable estimates, we also calculated ORs comparing the third and fourth quartiles of the index to the first and second combined (n = 12 cases). These ORs (95% CIs) were 1.5 (0.6-3.9; P = 0.46) and 2.2 (0.8-6.0; P = 0.12), respectively. The components most highly correlated with the specific DNAt2 inhibitor index were onions (r = 0.59), apples (r = 0.46), and canned beans (r = 0.44). Noncomponent foods were not notably correlated with this index.

Table 3 shows the associations of infant leukemia, overall and by subtype, with the VF+ index. There were statistically significant or near-significant inverse linear trends in risk of overall (P = 0.046), MLL+ (P = 0.064), and ALL(MLL+) (P = 0.01) infant leukemia with increasing values of the VF+ index. However, analysis of the VF+ index as a categorical variable suggested that leukemia risk did not decrease monotonically. The ORs (95% CIs) comparing the second to fourth quartiles of the VF+ index to the first were 0.6 (0.4-1.1), 0.6 (0.4-1.0), and 0.6 (0.4-1.1), respectively, for overall leukemia; 0.5 (0.3-0.9), 0.3 (0.2-0.7), and 0.6 (0.3-1.1), respectively, for MLL+ leukemia; and 0.6 (0.3-1.1), 0.2 (0.1-0.5), and 0.5 (0.2-0.9), respectively, for ALL(MLL+). Fresh fruits (r = 0.66), fresh vegetables (r = 0.69), and canned vegetables (r = 0.60) were the components most highly correlated with the VF+ index. Noncomponent foods also were not notably correlated with this index (data not shown).

We repeated the analyses of MLL+ and MLL− leukemia using only those cases whose MLL status was molecularly confirmed. Results were consistent with those obtained using the broader definition of MLL status (data not shown).

Discussion

This case-control study is the largest to date to investigate the specific hypothesis that *in utero* exposure to DNAt2 inhibitors increases the risk of MLL+ infant leukemia. We originally proposed this hypothesis based on the analogy to epipodophyllotoxin-related secondary AML(MLL+) (10, 11) and laboratory studies that address mechanisms of DNAt2 inhibition and MLL+ leukemia (5-7, 9, 30).

Table 1. Distribution of covariates of cases and controls

Covariates	Cases (n = 240)	Controls (n = 255)	P
Maternal factors			
Age, mean (SD)	29 (5.54)	30 (5.58)	0.06
Education (%)			
Less than college	43.9	38.8	0.25
College or more	56.1	61.2	
Race (%)			
White	79.5	85.5	0.003
Black	2.1	5.5	
Hispanic	10.5	3.5	
Other	8.0	5.5	
Household income (%)			
≤$30,000	36.9	31.9	0.03
$30,000-75,000	48.7	44.1	
>$75,000	14.4	24.0	
Smoke (%)	25.1	28.6	0.38
Drink (%)	65.6	69.4	0.36
Morning sickness (%)	70.4	62.8	0.07
Infant factors			
Male (%)	52.1	47.5	0.30
Birth weight (g), mean (SD)	3,537 (539)	3,447 (586)	0.08

Table 2. Adjusted ORs, 95% CIs, and Ps for linear trend for the specific DNAt2 inhibitor-containing food index

Quartile of specific DNAt2 inhibitor index	Controls	ALL		AML		ALL or AML	
		Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
MLL+							
Q1	59	28	1	4	1	32	1
Q2	67	17	0.5 (0.3-1.1)	8	1.9 (0.5-7.0)	25	0.7 (0.4-1.3)
Q3	65	22	0.7 (0.3-1.4)	8	2.1 (0.6-7.7)	30	0.9 (0.5-1.6)
Q4	64	16	0.5 (0.2-1.1)	9	3.2 (0.9-11.9)	25	0.7 (0.4-1.5)
P for trend			0.19		0.10		0.67
MLL−							
Q1	59	11	1	9	1	20	1
Q2	67	10	0.7 (0.3-1.9)	11	1.1 (0.4-3.1)	21	0.9 (0.4-2.0)
Q3	65	10	0.9 (0.4-2.5)	7	0.8 (0.3-2.4)	17	0.9 (0.4-1.9)
Q4	64	12	1.0 (0.4-2.8)	10	0.8 (0.3-2.4)	22	0.9 (0.4-2.0)
P for trend			0.83		0.23		0.52
MLL+/− and indeterminate							
Q1	59	46	1	19	1	65	1
Q2	67	30	0.5 (0.3-1.0)	26	1.3 (0.6-2.5)	56	0.7 (0.4-1.2)
Q3	65	37	0.7 (0.4-1.3)	20	1.0 (0.5-2.0)	57	0.8 (0.5-1.3)
Q4	64	35	0.7 (0.4-1.2)	26	1.2 (0.6-2.5)	61	0.8 (0.5-1.4)
P for trend			0.29		0.88		0.47

NOTE: ORs adjusted for mother's age at birth of index child, income, and education, and infant's race and sex.

Laboratory data also support the contention, which was the focus of this report, that some dietary inhibitors of DNAt2 act similarly to epipodophyllotoxins. Certain flavonoids (15, 16) and catechins (15) can induce DNA cleavage via DNAt2 and the former have been shown to induce cleavage of the MLL locus in vitro (17). Three case-control studies are relevant as well. Two showed that a low activity variant of the *NQO1* gene, the product of which detoxifies metabolites of flavonoids, is preferentially associated with MLL+ infant leukemia (19, 20). The association was particularly pronounced for ALL(MLL+) with the t(4;11) translocation. The second was our preliminary study from the Children's Cancer Group, which showed increasing risk estimates for infant AML, for but not ALL, with increasing maternal consumption of some foods that contain DNAt2 inhibitors (P for trend = 0.04; ref. 18).

The results of the current analysis show similarities to those of our earlier report in that elevated risks were seen only among infant AML. However, in the earlier report, no data were collected on onion, berry, or apple consumption; the index variable included fruit and vegetable consumption instead because they included a subset of foods that contain DNAt2 inhibitors. The index of the previous study was thus constructed similarly to our VF+ index. We did not find an association of AML with the VF+ index in contrast with those of the earlier report (although the previous study included only 30 AML cases and the ORs were very imprecise).

In the present analysis, risk of AML(MLL+) seemed to increase with increasing values of the specific DNAt2 inhibitor index. However, this observation is based on only 29 cases, resulting in wide 95% CIs and a P for linear trend of 0.10. The small number of cases in this critical leukemia subtype represents a major limitation of the study. On the other hand, a lack of any such suggestive positive trend in the risk of other leukemia subgroups with increasing values of the specific DNAt2 inhibitor index diminishes the possibility that the finding regarding AML(MLL+) was due to measurement error, selection, or confounding.

Accuracy of dietary recall is a potential source of misclassification. There is a general tendency to report current rather than past consumption when recalling maternal diet during pregnancy (31). In addition, our dietary instrument imperfectly assessed fetal exposure to dietary DNAt2 inhibitors. For instance, we did not account for the differing bioavailability and bioactivity of the dietary DNAt2 inhibitors because our

Table 3. Adjusted ORs, 95% CIs, and Ps for linear trend for the VF+ index

Quartile of VF+ index	Controls	ALL		AML		ALL or AML	
		Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
MLL+							
Q1	53	32	1	9	1	41	1
Q2	67	22	0.6 (0.3-1.1)	2	0.2 (0.0-0.9)	24	0.5 (0.2-0.9)
Q3	68	11	0.2 (0.1-0.5)	8	0.7 (0.2-1.9)	19	0.3 (0.2-0.6)
Q4	67	18	0.5 (0.2-0.9)	10	1.1 (0.4-2.9)	28	0.6 (0.3-1.1)
P for trend			0.01		0.57		0.06
MLL−							
Q1	53	8	1	11	1	19	1
Q2	67	13	1.2 (0.4-3.3)	9	0.6 (0.2-1.6)	22	0.8 (0.4-1.7)
Q3	68	11	1.1 (0.4-3.0)	10	0.7 (0.3-1.9)	21	0.9 (0.4-1.9)
Q4	67	11	1.0 (0.4-2.9)	7	0.5 (0.2-1.3)	18	0.7 (0.3-1.4)
P for trend			0.96		0.09		0.27
MLL+/− and indeterminate							
Q1	53	46	1	25	1	71	1.0
Q2	67	37	0.7 (0.4-1.2)	20	0.6 (0.3-1.2)	57	0.6 (0.4-1.0)
Q3	68	28	0.5 (0.3-0.9)	27	0.8 (0.4-1.6)	55	0.6 (0.4-1.0)
Q4	67	37	0.7 (0.4-1.2)	19	0.6 (0.3-1.2)	56	0.6 (0.4-1.0)
P for trend			0.09		0.18		0.05

NOTE: ORs adjusted for mother's age at birth of index child, income, and education, and infant's race and sex.

instrument did not distinguish between varieties of foods (e.g., *Vidalia* versus red onions), which can differ in DNAt2 inhibitor content, and because data on the relative level of DNAt2 inhibition of each substance were lacking (14, 32). Inability to adjust for changes in food consumption during pregnancy, other than for beverages, and to adjust for total energy intake may also have contributed to measurement error (33). We did not control for the presence of polymorphisms in genes whose products affect the bioavailability of DNAt2 inhibitors or collect data on exposure to other substances that alter DNAt2 function (34). Lastly, the relatively low response rates of our random digit dialing controls (67% screening and 59% field response rate) raise the potential of selective enrollment, particularly with respect to socioeconomic status. Families of controls were significantly wealthier than were those of cases, although we note that there was no significant difference in maternal education. Notwithstanding the possibility of these biases, it is difficult to conceive how they would act together to produce a specific association with AML(MLL+) infant leukemia in particular.

Somewhat unexpectedly, we found a significant *inverse* association of increasing consumption of fresh vegetables and fruits (VF+ index) with overall leukemia and with several subgroups. Interestingly, among the AML(MLL+) group, we observed a significant inverse association of the second quartile of the VF+ index compared with the first, whereas the comparisons of the third and fourth quartiles to the first were null. This perhaps suggests that high consumption of DNAt2 inhibitor-containing fruits and vegetables diminishes the benefit of high consumption of other fruits and vegetables. Inverse associations of fresh fruit and vegetable intake have been noted with a variety of adult (35) and childhood (36) cancers. Because consumption of fruits and vegetables increases with measures of socioeconomic status, such as maternal education and household income (37, 38), selection bias may explain the associations in many studies (35). In this analysis, we adjusted for maternal education and household income, which had little effect on point estimates, but we cannot rule out residual confounding. However, because this observation may reflect a true protective effect of maternal fruit and vegetable consumption, it may still be the basis for further study.

Overall, this study provides encouraging evidence that maternal vegetable and fruit consumption decreases the overall risk of infant leukemia. In contrast, consumption of specific foods containing compounds that interfere with DNAt2 may increase the risk of AML(MLL+) infant leukemia, which is analogous to the observed involvement of DNAt2-targeted cytotoxic drugs in therapy-related cases. Our epidemiologic analyses also provide support for distinct pathways in the etiology of subtypes of infant leukemia.

Acknowledgments

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