Maternal Immunoglobulin E and Childhood Leukemia

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Abstract

Childhood leukemia, particularly acute lymphoblastic leukemia (ALL), has long been hypothesized to be affected by abnormal immune responses to microbial challenges stemming from a lack of immune modulation in early childhood. Studies of allergies suggest that a child's immune development may be modulated by maternal immune status. We conducted a study to explore the relationship between maternal immunoglobulin E (IgE) and childhood leukemia and to investigate whether maternal immune status can influence childhood leukemia risk. Serum total and specific IgE (respiratory and food) were measured in biological mothers of 352 children (193 healthy controls and 159 leukemia cases, including 139 ALL cases) ages <8 years who were enrolled in the Northern California Childhood Leukemia Study. Odds ratios associated with maternal IgE were calculated using unconditional logistic regression adjusted for child's age, sex, race/ethnicity, and annual household income. A positive association between childhood leukemia or ALL and elevated levels of maternal serum total IgE was observed, especially among Hispanics. In addition, a positive association was observed between childhood leukemia or ALL and maternal respiratory or food IgE status. These results suggest that maternal immune function may play a crucial role in the etiology of childhood leukemia, although additional studies need to be conducted to confirm the results of this study and provide a perspective on mechanisms. (Cancer Epidemiol Biomarkers Prev 2009;18(8):2221–7)

Introduction

Childhood leukemia, particularly acute lymphoblastic leukemia (ALL), has long been hypothesized to have an infectious etiology. Both Kinlen's "population mixing" (1) and Greaves' "delayed infection" (2) hypotheses propose that childhood leukemia may result from abnormal responses to microbial challenges due to lack of immune priming during early childhood, similar to the "hygiene hypothesis" proposed by Strachan to explain the increasing prevalence of allergies in the western population (3). Allergy, mostly associated with an elevated level of serum immunoglobulin E (IgE; atopic allergy), is caused by hyperactive immune responses to environmental antigenic challenges. IgE is a key initiator of atopic allergy. When the IgE antibodies bound to the high-affinity Fc receptors on mast cells or basophils are cross-linked by antigens, a cascade of events occurs resulting in the release of immune mediators causing allergic symptoms (4).

Both allergy and childhood leukemia have been inversely associated with higher birth order (5-11) and early daycare attendance (12-17), which is consistent with the "hygiene hypothesis." Most studies to date on childhood leukemia have focused on postnatal immune challenges using measures such as daycare attendance, birth order, infectious events, and vaccination. However, recent studies of children with allergies showed that a child's immune development begins *in utero* and may be modulated by the mother's immune status (18-20). We conducted a study on the association between maternal IgE and childhood leukemia to investigate the influence of maternal immune status on childhood leukemia risk.

Materials and Methods

Study Subjects. Subjects of this analysis were recruited by the Northern California Childhood Leukemia Study (NCCLS). The NCCLS is an ongoing case-control study that started in 1995 and recruits subjects from 35 counties in northern and central California. Case subjects newly diagnosed with leukemia are recruited from nine hospitals usually within 72 h of diagnosis. Birth certificate information obtained from California Office of Vital Records is used to select one or two controls for each case, matching on age, sex, Hispanic ethnicity, and maternal race. The eligibility criteria for all subjects are (*a*) being a resident of the study area, (*b*) being ages <15 years at case diagnosis (reference date for the matched controls), (*c*) having at least one English- or Spanish-speaking parent or guardian, and (*d*) having not been previously diagnosed with cancer. For this study, biological mothers of 352 children (193 healthy controls and 159 leukemia cases, including 139 ALL cases) ages <8 years who were enrolled in the NCCLS between August 2000 and December 2007 were asked to provide blood samples. The interval between child's birth and maternal blood collection ranged from 8 months to 10.8 years with median of 5.1 years.

IgE Measurements. Serum total and specific IgE (respiratory and food) were measured using Phadia

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ImmunoCAP assay (Phadia) in several steps: (*a*) incubation of 40 μL maternal serum on the mix of allergens or anti-IgE antibodies bound to solid-phase ImmunoCAP; (*b*) incubation with enzyme-labeled antibodies, where antibodies against the heavy chains (constant regions) of IgE were used for the total IgE test and antibodies against the light chains (variable regions) of IgE were used for the specific allergen tests; and (*c*) incubation with developer and stop solutions. The respiratory IgE panel (Phadiotop) included 15 allergens that identify 97% of atopic allergy to respiratory allergens. The food panel tested six allergens that included most food allergies (peanut, tree nut, shellfish, milk, egg, and codfish). For analysis purposes, those with undetectable IgE levels were assigned values halfway between zero and the detection limit (1 kU/L for total IgE and 0.17 kU/L for respiratory or food IgE). Total IgE was categorized into three groups: <25 kU/L = normal, 25 to 100 kU/L = borderline, and >100 kU/L = elevated (21). Respiratory and food IgE were categorized into two groups: ≤0.35 kU/L = negative and >0.35 kU/L = positive (22). These are the established cut points used for clinical decision-making. For quality control, 21 samples were selected at random for duplicate measurements and the results were 100% concordant with regards to the clinical classifications. Spearman correlations for the duplicate measurements were 0.999, 1.0, and 0.997 for total IgE, respiratory IgE, and food IgE, respectively. In addition, laboratory personnel were blinded to case-control status of maternal specimens.

Statistical Analysis. Univariate analyses were done to compare the distribution of child's sex, child's race/ethnicity, child's age at diagnosis/reference date, mother's age at child's birth, annual household income, parental smoking, and maternal serum IgE between cases and controls using χ^2 tests (for categorical variables) and *t* tests (for continuous variables). Multivariable logistic regression adjusted for child's age, sex, race/ethnicity, and annual household income was done to assess the association between maternal IgE and childhood leukemia. Although a positive association between cigarette smoking and serum IgE has been documented (23), adjusting for smoking variables had minimal effect (*P* values for coefficients of these variables ranged from 0.30 to 0.61) on our results; therefore, we excluded the smoking variables from statistical models in the final analyses. The total IgE, respiratory IgE, and food IgE variables were included in the multivariable regression model as categorical variables as described in the previous section. A test for trend was done for total IgE by coding it as an ordinal variable: 0 = normal, 1 = borderline, and 2 = elevated. In addition, total IgE was $\log_{10}$ transformed and analyzed in the multivariable regression models as a continuous variable. Analyses were first done with all leukemia cases and all controls and then again with only the ALL cases and all controls. Sensitivity analyses were done to assess the effect of timing of maternal serum collection, comparing the association between maternal IgE and childhood leukemia among maternal serum samples collected closer to the time of birth versus those collected farther from the time of birth. This was done by first calculating the time (in years) between maternal blood collection and child's birth. A product term between maternal blood collection time and maternal IgE variable was then included in the statistical model to evaluate the influence of maternal blood collection time on maternal IgE-childhood leukemia association. The significance of the product term was assessed using the log-likelihood ratio test comparing the full model with the product term to the submodel without the product term.

Additional analyses for ALL were done stratified on race/ethnicity (Hispanic versus non-Hispanic White) and sex. Differences in the association between maternal serum IgE and childhood ALL by strata were assessed by including a product term (maternal IgE × Hispanic status or maternal IgE × sex) in the regression model, and the test for interaction was done using the log-likelihood ratio test comparing the full model with the product term to the submodel without the product term.

Results

The distributions of child's sex, race/ethnicity, age, mother's age, and parental smoking were similar between cases and controls (Table 1). Controls had higher levels of annual household income compared with cases. Serum total IgE, respiratory IgE, and food IgE were all higher among case mothers than among control mothers in the univariate analyses.

In the multivariable analyses, the risk of childhood leukemia increases with the level of maternal IgE (Table 2). Children of mothers classified as having borderline and elevated total IgE had a 1.3- and 1.8-fold increased risk of leukemia, respectively (P_{trend} = 0.04). Similarly, a positive dose-relationship was seen between childhood leukemia and the $\log_{10}$-transformed maternal total IgE, although this was not statistically significant. Children whose mothers were positive for respiratory IgE or food IgE had an elevated risk for childhood leukemia, although the association was only statistically significant (*P* = 0.03) for food IgE. When the multivariable analyses were restricted to ALL cases and all controls, all of the positive associations with maternal total, respiratory, or food IgE became stronger and statistically significant (*P* < 0.05).

Analyses stratified on race/ethnicity status (Hispanic versus non-Hispanic White) showed that the positive association between maternal total IgE and childhood ALL is present only among Hispanics (Table 3). In contrast, the positive association between maternal respiratory IgE or food IgE and childhood ALL did not differ significantly between Hispanics and non-Hispanic Whites.

Analyses stratified on sex did not show any statistically significant difference in the positive association between maternal total IgE, respiratory IgE, or food IgE and childhood ALL between males and females (Table 4).

Sensitivity analyses comparing the association between maternal IgE and childhood leukemia among maternal serum samples collected closer to the time of birth versus those collected farther from time of birth did not indicate any significant difference (*P* values = 0.66-0.92). In addition, there was no correlation between maternal blood collection time and maternal total IgE (Pearson correlation coefficient = -0.03; *P* = 0.62).

Discussion

The current analysis indicates that mothers of children with childhood leukemia, particularly childhood ALL,

Table 1. Comparisons of demographic characteristics, parental smoking, and maternal IgE between cases (159 cases of all leukemia types and 139 cases of ALL) and 193 controls; the NCCLS, 2000-2007

	Control (n = 193)	All leukemia types (n = 159)		ALL (n = 139)	
	n (%)	n (%)	P*	n (%)	P*
Child's sex					
Male	117 (60.6)	95 (59.7)	0.87	82 (59.0)	0.77
Female	76 (39.4)	64 (40.3)		57 (41.0)	
Child's race/ethnicity					
Hispanic	90 (46.6)	76 (47.8)	0.60	65 (46.8)	0.46
Non-Hispanic White	68 (35.3)	49 (30.8)		42 (30.2)	
Other	35 (18.1)	34 (21.4)		32 (23.0)	
Child's age					
Mean (SE)	3.87 (0.13)	3.82 (0.15)	0.83	3.93 (0.15)	0.77
Mother's age					
Mean (SE)	30.46 (0.42)	29.38 (0.54)	0.11	29.25 (0.55)	0.07
Annual household income					
<15,000	17 (8.8)	30 (18.9)	0.02	26 (18.7)	0.02
15,000-29,999	18 (9.3)	16 (10.1)		15 (10.8)	
30,000-44,999	22 (11.4)	23 (14.5)		20 (14.4)	
45,000-59,999	24 (12.4)	26 (16.3)		23 (16.6)	
60,000-74,999	15 (7.8)	7 (4.4)		6 (4.3)	
≥75,000	97 (50.3)	57 (35.8)		49 (35.2)	
Parental smoking					
Maternal, ever					
No	140 (72.5)	125 (78.6)	0.19	109 (78.4)	0.22
Yes	53 (27.5)	34 (21.4)		30 (21.6)	
Maternal, now					
No	182 (94.3)	152 (95.6)	0.58	133 (95.7)	0.57
Yes	11 (5.7)	7 (4.4)		6 (4.3)	
Maternal, postnatal					
No	180 (93.3)	147 (92.5)	0.77	127 (91.4)	0.52
Yes	13 (6.7)	12 (7.5)		12 (8.6)	
Paternal, ever					
No	128 (66.3)	95 (60.1)	0.23	85 (61.6)	0.38
Yes	65 (33.7)	63 (39.9)		53 (38.4)	
Paternal, now					
No	168 (88.0)	133 (85.3)	0.46	120 (87.6)	0.92
Yes	23 (12.0)	23 (14.7)		17 (12.4)	
Others, postnatal†					
No	190 (98.4)	153 (96.8)	0.31	137 (98.6)	0.93
Yes	3 (1.6)	5 (3.2)		2 (1.4)	
Maternal IgE					
Total IgE‡					
Normal	89 (46.1)	55 (34.6)	0.05	45 (32.3)	0.02
Borderline	69 (35.8)	62 (39.0)		54 (38.9)	
Elevated	35 (18.1)	42 (26.4)		40 (28.8)	
Log_{10} total IgE, mean (SE)	1.48 (0.05)	1.62 (0.05)	0.04	1.66 (0.06)	0.01
Respiratory IgE§					
Negative	121 (62.7)	86 (54.1)	0.10	70 (50.4)	0.02
Positive	72 (37.3)	73 (45.9)		69 (49.6)	
Food IgE§					
Negative	188 (97.4)	146 (91.8)	0.02	126 (90.7)	0.007
Positive	5 (2.6)	13 (8.2)		13 (9.3)	

*P values were calculated using χ^2 tests (for categorical variables) and t tests (for continuous variables).
†The presence of smokers other than the mother in the household from child's birth until child's third birthday or the date of diagnosis (reference date for the control).
‡<25 kU/L = normal; 25-100 kU/L = borderline; and >100 kU/L = elevated.
§≤0.35 kU/L = negative and >0.35 kU/L = positive.

had elevated levels of serum total IgE. This effect was largely limited to Hispanics in our study. In addition, a positive association was observed between childhood leukemia or ALL with maternal respiratory or food IgE status.

Maternal IgE has been strongly linked to cord blood, infant, and child IgE levels and the development of childhood allergies (24-26). Given the preponderance of studies and prevailing wisdom that allergies are protective against childhood leukemias, it is somewhat incongruous that case mothers exhibited higher IgE levels than control mothers in our study, as higher IgE levels in case mothers should impart a higher risk for allergies in cases. The significant results in our study are counter to what would be hypothesized and should stimulate further studies of this association to explore possible mechanistic explanations. It is not known what maternal IgE levels represent besides simply being markers of allergy in children.

First of all, IgE is only a predictor of atopic allergy and an inadequate one at that (27, 28); in addition, IgE is not involved with nonatopic allergies. It is possible that maternal IgE here is serving as a marker of maternal immune status and *in utero* immune modulation affecting different immune pathways irrespective of allergy. Support of maternal modulation of a child's immune development has been observed in several biological studies. A study by Amoudruz et al. suggests a decreased response to microbial challenges in children whose mothers have allergies;

Table 2. Maternal IgE among 193 controls versus childhood leukemia (*n* = 159) or ALL (*n* = 139); the NCCLS, 2000-2007

	Controls (*n* = 193)	All leukemia types (*n* = 159)			ALL (*n* = 139)		
	n (%)	*n* (%)	OR (95% CI)*	*P*	*n* (%)	OR (95% CI)*	*P*
Total IgE†							
Normal	89 (46.1)	55 (34.6)	Reference		45 (32.3)	Reference	
Borderline	69 (35.8)	62 (39.0)	1.33 (0.81-2.19)	0.27	54 (38.9)	1.42 (0.84-2.39)	0.19
Elevated	35 (18.1)	42 (26.4)	1.83 (1.02-3.28)	0.04	40 (28.8)	2.14 (1.17-3.94)	0.01
Trend			1.35 (1.01-1.80)	0.04		1.46 (1.08-1.97)	0.01
Log_{10} total IgE			1.37 (0.96-1.94)	0.08		1.50 (1.04-2.16)	0.03
Respiratory IgE‡							
Negative	121 (62.7)	86 (54.1)	Reference		70 (50.4)	Reference	
Positive	72 (37.3)	73 (45.9)	1.43 (0.92-2.21)	0.11	69 (49.6)	1.64 (1.04-2.58)	0.03
Food IgE‡							
Negative	188 (97.4)	146 (91.8)	Reference		126 (90.7)	Reference	
Positive	5 (2.6)	13 (8.2)	3.34 (1.15-9.76)	0.03	13 (9.3)	3.98 (1.35-11.71)	0.01

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
*ORs were adjusted for child's age, sex, race/ethnicity, and annual household income using unconditional logistic regression.
†<25 kU/L = normal; 25-100 kU/L = borderline; and >100 kU/L = elevated.
‡≤0.35 kU/L = negative and >0.35 kU/L = positive.

a lower expression of toll-like receptor-2 and -4 of the cord blood mononuclear cells and a lower peptidoglycan-stimulated response of interleukin-6 were observed in children of mothers with allergy compared with those of children whose mothers had no allergies (18). Schaub et al. reported lower expression of Foxp3 and lower levels of interleukin-10 and IFN-γ among children with atopic mothers, suggesting impairment of T-regulatory cell function among neonates with atopic mothers (19, 20). T-regulatory cells keep immune function in check and prevent damages due to hyperactive immune responses. The reduced activity of T-regulatory cells may result in overactive Th1 and Th2 function and may explain the concurrent increase in the prevalence of both allergic and autoimmune diseases in the developed countries (29). Similarly, the influence of maternal immune status on a child's immune development early in life may determine a child's immune response to microbial challenges, which if abnormal, may lead to the development of childhood leukemia.

Because the heritability of total IgE levels was estimated by a twin study to be ~65% (30), high maternal IgE level may predict a child's tendency to have high serum IgE. The positive association observed in our study between maternal IgE and childhood leukemia implies that the same positive association may exist between child's IgE and childhood leukemia. However, this is inconsistent with the majority of the studies that have examined the risk of childhood leukemia associated with childhood allergies (7 of 7 interview-based studies and 1 of 2 medical record–based studies, all case-control in design), which showed an inverse association (31-39).

There may be several explanations for this discrepancy: (*a*) Although maternal and children's IgE levels are related, they are not 100% concordant because a mother and her child share only 50% of the genetic material, and environmental factors can also strongly influence allergic sensitization (40). (*b*) A substantial proportion of people with allergies do not have elevated IgE levels (nonatopic allergy; ref. 41); therefore, serum IgE and allergic symptoms, although related, are not the same. (*c*) Seven of the 8 studies that reported a inverse association between children's allergies and childhood leukemia were based on self-reported histories of allergies lacking a rigorous definition or diagnosis, and reporting errors/biases could have been an issue. The only study that reported a

Table 3. Maternal IgE and childhood ALL, Hispanic (65 cases and 90 controls) versus non-Hispanic White (42 cases and 68 controls); the NCCLS, 2000-2007

	Hispanic			Non-Hispanic White			$P_{interaction}$
	Cases/controls	OR (95% CI)*	*P*	Cases/controls	OR (95% CI)*	*P*	
Total IgE†							
Normal	15/40	Reference		24/36	Reference		0.09
Borderline	25/33	1.67 (0.74-3.79)	0.22	14/22	0.91 (0.38-2.14)	0.82	
Elevated	25/17	3.51 (1.44-8.54)	0.006	4/10	0.66 (0.18-2.39)	0.53	
Trend		1.87 (1.20-2.92)	0.006		0.84 (0.48-1.48)	0.55	0.03
Log_{10} total IgE		1.87 (1.06-3.31)	0.03		0.92 (0.50-1.70)	0.79	0.09
Respiratory IgE‡							
Negative	33/60	Reference		21/42	Reference		0.86
Positive	32/30	1.87 (0.95-3.69)	0.07	21/26	1.69 (0.76-3.74)	0.20	
Food IgE‡							
Negative	61/89	Reference		37/64	Reference		0.37
Positive	4/1	6.07 (0.65-56.67)	0.11	5/4	2.17 (0.53-8.87)	0.28	

*ORs were adjusted for child's age, sex, and annual household income using unconditional logistic regression.
†<25 kU/L = normal; 25-100 kU/L = borderline; and >100 kU/L = elevated.
‡≤0.35 kU/L = negative and >0.35 kU/L = positive.

Table 4. Maternal IgE and childhood ALL, male (82 cases and 117 controls) versus female (57 cases and 76 controls); the NCCLS, 2000-2007

	Male			Female			$P_{interaction}$
	Cases/controls	OR (95% CI)*	*P*	Cases/controls	OR (95% CI)*	*P*	
Total IgE†							
Normal	25/51	Reference		20/38	Reference		0.98
Borderline	35/45	1.45 (0.74-2.85)	0.28	19/24	1.32 (0.56-3.08)	0.52	
Elevated	22/21	2.05 (0.92-4.56)	0.08	18/14	2.21 (0.85-5.75)	0.10	
Trend		1.43 (0.97-2.13)	0.07		1.47 (0.92-2.36)	0.11	0.96
Log_{10} total IgE		1.53 (0.94-2.48)	0.09		1.46 (0.83-2.56)	0.19	0.78
Respiratory IgE‡							
Negative	41/73	Reference		29/48	Reference		
Positive	41/44	1.75 (0.97-3.14)	0.06	28/28	1.45 (0.70-3.03)	0.32	0.72
Food IgE‡							
Negative	74/113	Reference		52/75	Reference		
Positive	8/4	3.49 (0.99-12.35)	0.05	5/1	6.24 (0.65-59.64)	0.11	0.63

*ORs were adjusted for child's age, race/ethnicity, and annual household income using unconditional logistic regression.
†<25 kU/L = normal; 25-100 kU/L = borderline; and >100 kU/L = elevated.
‡≤0.35 kU/L = negative and >0.35 kU/L = positive.

positive association between childhood leukemia and allergic conditions used medical record data (37), although the opposite was reported by another medical record-based study (39). (*d*) The inverse association between allergy and childhood leukemia may be due to reverse causality. There is evidence indicating that patients with hematologic malignancies may have lower immunocompetence (42, 43), and it is possible that children in the process of developing leukemia may have lower prevalence of atopy due to immune dysfunction. (*e*) A final speculative explanation to reconcile the historical leukemia epidemiology and maternal IgE data here is that children with leukemia are nonatopic children of atopic mothers, and the mismatch in allergic phenotype is diagnostic of an "at-risk" aberrantly modulated immune system. A child who is genetically and environmentally programmed to develop allergy but does not develop allergy might also be unable to react properly to nascent tumor cells, leading to increased risk of leukemia. Testing of this hypothesis would require detailed information and biological specimens collected from parents and children before diagnosis, including maternal blood samples collected during pregnancy.

We observed a difference in the association between maternal serum total IgE and childhood ALL between Hispanics and non-Hispanic Whites, with the association being significant only among Hispanics. Whether this difference is due to genetic or environmental factors is not clear and further investigation is required. A difference in the association between immune factors and childhood ALL by Hispanic ethnicity was previously reported by our study (17). In that study, we observed an inverse association between daycare attendance (used as a surrogate for potential of infection) and childhood ALL and between ear infection during infancy and childhood common ALL among non-Hispanic White children but not among Hispanic children (17). A study by Litonjua et al. showed that, compared to White women, Hispanic women had higher serum total IgE and were more likely to be sensitized to alloallergens, and the differences were explained more by race/ethnicity than socioeconomic status measures (44). Similarly, in our study, Hispanic control mothers had higher level of total IgE compared to Caucasian control mothers (mean log_{10} total IgE for Hispanic control mothers versus non-Hispanic White control mothers = 1.6 versus 1.3; $P = 0.002$). It is possible that a threshold effect may exist, which could explain at least partially the lack of association between maternal total IgE (as a proxy for maternal immune status) and childhood ALL among non-Hispanic Whites. Another study reported that neonatal cord blood IgE, a predictor of atopy, is higher among Hispanics compared to non-Hispanic Whites, independent of two other predictors of cord blood IgE, maternal total IgE level and socioeconomic status (24). This suggests that genetic differences may also contribute to the disparate results observed between Hispanics and non-Hispanic Whites. In addition, there may be differences in environmental exposures between Hispanics and non-Hispanic Whites that contribute to the complex immune development process, which involves an interplay between genetic traits and environmental exposures.

The results of this study must be interpreted in the context of several limitations. First, the number of mothers tested positive for food IgE was small, which yielded less stable results with wide confidence intervals, and not statistically significant (although positive associations were still observed) in the stratified analyses by ethnicity and gender. However, the positive association between maternal food IgE and childhood leukemia was consistent with the results for total and respiratory IgE.

Second, maternal blood was collected after child's leukemia diagnosis (reference date for the controls) and not during pregnancy such that the maternal IgE status measured may not represent the maternal IgE status during pregnancy. It is assumed, however, that the relative IgE level will remain the same during and after pregnancy, that is, those mothers with higher levels of IgE are also the ones with higher levels of IgE during pregnancy (45). This assumption is supported by our sensitivity analysis, which showed that the association between maternal IgE and childhood leukemia did not differ by the timing of maternal serum collection after a child's birth.

Third, we did not collect self-reported allergy information from mothers and were thus not able to identify mothers with nonatopic allergies. It is possible that maternal nonatopic allergies may have a similar influence on childhood leukemia risk as maternal atopic allergies; however, if such were the case, not accounting for nonatopic allergies as risk factors would have biased our results toward the null. Also, although we did not measure paternal IgE,

studies show that the atopic status of the children appeared to correlate more with maternal atopy than with paternal atopy (25, 46-48), suggesting that maternal factors are more important in modulating children's immune development. Finally, we did not have sufficient data on allergy or atopy of the case and control children. Despite these limitations, this is the first study to assess the effect of maternal immune factors on the development of childhood leukemia, and the results are valuable in generating hypotheses as well as emphasize the importance of the prenatal period in studying the role of infection and immunity in the etiology of childhood leukemia.

In summary, the current study showed that high maternal IgE levels were positively associated with childhood leukemia. These results suggest that maternal immune function may play a crucial role in the etiology of childhood leukemia. To further test this hypothesis, we plan to conduct several studies in the future. (*a*) We plan to study germ-line polymorphisms in the immune function genes of the mothers and their association to the childhood leukemia risk. The maternal germ-line genetic variations are not subject to recall error/bias and are present before the child's diagnosis of leukemia and thus more interpretable for the causal relationship. (*b*) We will perform maternal-fetal analysis (49) using data of the immune function genetic polymorphisms of both the mother and the child to assess the independent contributions by the maternal immune status and the child's own immune development to childhood leukemia risk. (*c*) Cytokine profiles in the neonatal dried blood spots will be measured using a validated technique (50-52) and comparisons will be made between childhood leukemia cases and healthy controls. The cytokine profile at birth is influenced by multiple factors including a child's genetic makeup, maternal genetic influences, and *in utero* exposures to various environmental factors, thus serving as a powerful indicator of a child's baseline immune function at birth, which encompasses *in utero* gene-environment interaction.

All of the above-mentioned studies may also offer additional clues to explain the difference by Hispanic status in the association between maternal total IgE and childhood ALL. In the future in California, it will be possible to access maternal blood specimens for cases and controls collected during pregnancy for α-fetoprotein screening. This would represent an excellent source of prediagnostic maternal specimens to explore some of the above questions. By extending the assessment of children's immune development to include the pregnancy period, the role of immune function in the development of childhood leukemia can be more comprehensively assessed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. Lancet 1988;2:1323–7.
2. Greaves MF. Speculations on the cause of childhood acute lymphoblastic leukemia. Leukemia 1988;2:120–5.
3. Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299:1259–60.
4. Gould HJ, Sutton BJ, Beavil AJ, et al. The biology of IGE and the basis of allergic disease. Annu Rev Immunol 2003;21:579–628.
5. Westergaard T, Rostgaard K, Wohlfahrt J, Andersen PK, Aaby P, Melbye M. Sibship characteristics and risk of allergic rhinitis and asthma. Am J Epidemiol 2005;162:125–32.
6. Bernsen RM, de Jongste JC, van der Wouden JC. Birth order and sibship size as independent risk factors for asthma, allergy, and eczema. Pediatr Allergy Immunol 2003;14:464–9.
7. Lewis SA, Britton JR. Consistent effects of high socioeconomic status and low birth order, and the modifying effect of maternal smoking on the risk of allergic disease during childhood. Respir Med 1998;92:1237–44.
8. Matricardi PM, Franzinelli F, Franco A, et al. Sibship size, birth order, and atopy in 11,371 Italian young men. J Allergy Clin Immunol 1998;101:439–44.
9. Strachan DP, Taylor EM, Carpenter RG. Family structure, neonatal infection, and hay fever in adolescence. Arch Dis Child 1996;74:422–6.
10. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol 2001;30:1428–37.
11. Westergaard T, Andersen PK, Pedersen JB, et al. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. J Natl Cancer Inst 1997;89:939–47.
12. Haby MM, Marks GB, Peat JK, Leeder SR. Daycare attendance before the age of two protects against atopy in preschool age children. Pediatr Pulmonol 2000;30:377–84.
13. Gilham C, Peto J, Simpson J, et al. Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study. BMJ 2005;330:1294.
14. Kramer U, Heinrich J, Wjst M, Wichmann HE. Age of entry to day nursery and allergy in later childhood. Lancet 1999;353:450–4.
15. Ma X, Buffler PA, Selvin S, et al. Daycare attendance and risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2002;86:1419–24.
16. Perrillat F, Clavel J, Auclerc MF, et al. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. Br J Cancer 2002;86:1064–9.
17. Ma X, Buffler PA, Wiemels JL, et al. Ethnic difference in daycare attendance, early infections, and risk of childhood acute lymphoblastic leukemia. Cancer Epidemiol Biomarkers Prev 2005;14:1928–34.
18. Amoudruz P, Holmlund U, Malmstrom V, et al. Neonatal immune responses to microbial stimuli: is there an influence of maternal allergy? J Allergy Clin Immunol 2005;115:1304–10.
19. Schaub B, Campo M, He H, et al. Neonatal immune responses to TLR2 stimulation: influence of maternal atopy on Foxp3 and IL-10 expression. Respir Res 2006;7:40.
20. Schaub B, Liu J, Hoppler S, et al. Impairment of T-regulatory cells in cord blood of atopic mothers. J Allergy Clin Immunol 2008;121:1491–9, 9 e1–13.
21. Zetterstrom O, Johansson SG. IgE concentrations measured by PRIST in serum of healthy adults and in patients with respiratory allergy. A diagnostic approach. Allergy 1981;36:537–47.
22. Yunginger JW, Ahlstedt S, Eggleston PA, et al. Quantitative IgE antibody assays in allergic diseases. J Allergy Clin Immunol 2000;105:1077–84.
23. Sherrill DL, Halonen M, Burrows B. Relationships between total serum IgE, atopy, and smoking: a twenty-year follow-up analysis. J Allergy Clin Immunol 1994;94:954–62.
24. Scirica CV, Gold DR, Ryan L, et al. Predictors of cord blood IgE levels in children at risk for asthma and atopy. J Allergy Clin Immunol 2007;119:81–8.
25. Liu CA, Wang CL, Chuang H, Ou CY, Hsu TY, Yang KD. Prenatal prediction of infant atopy by maternal but not paternal total IgE levels. J Allergy Clin Immunol 2003;112:899–904.

26. Canfield SM, Jacobson JS, Perzanowski MS, et al. Total and specific IgE associations between New York City Head Start children and their parents. J Allergy Clin Immunol 2008;121:1422–7, 7 e1–4.
27. Burrows B, Martinez FD, Cline MG, Lebowitz MD. The relationship between parental and children's serum IgE and asthma. Am J Respir Crit Care Med 1995;152:1497–500.
28. Klink M, Cline MG, Halonen M, Burrows B. Problems in defining normal limits for serum IgE. J Allergy Clin Immunol 1990;85:440–4.
29. Romagnani S. The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both? Immunology 2004;112:352–63.
30. Ahmadi KR, Lanchbury JS, Reed P, et al. Novel association suggests multiple independent QTLs within chromosome 5q21-33 region control variation in total humans IgE levels. Genes Immun 2003;4:289–97.
31. Nishi M, Miyake H. A case-control study of non-T cell acute lymphoblastic leukaemia of children in Hokkaido, Japan. J Epidemiol Community Health 1989;43:352–5.
32. Petridou E, Trichopoulos D, Kalapothaki V, et al. The risk profile of childhood leukaemia in Greece: a nationwide case-control study. Br J Cancer 1997;76:1241–7.
33. Schuz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Association of childhood leukaemia with factors related to the immune system. Br J Cancer 1999;80:585–90.
34. Wen W, Shu XO, Linet MS, et al. Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States). Cancer Causes Control 2000;11:303–7.
35. Schuz J, Morgan G, Bohler E, Kaatsch P, Michaelis J. Atopic disease and childhood acute lymphoblastic leukemia. Int J Cancer 2003;105: 255–60.
36. Jourdan-Da Silva N, Perel Y, Mechinaud F, et al. Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. Br J Cancer 2004;90:139–45.
37. Spector L, Groves F, DeStefano F, et al. Medically recorded allergies and the risk of childhood acute lymphoblastic leukaemia. Eur J Cancer 2004;40:579–84.
38. Rosenbaum PF, Buck GM, Brecher ML. Allergy and infectious disease histories and the risk of childhood acute lymphoblastic leukaemia. Paediatr Perinat Epidemiol 2005;19:152–64.
39. Hughes AM, Lightfoot T, Simpson J, et al. Allergy and risk of childhood leukaemia: results from the UKCCS. Int J Cancer 2007;121:819–24.
40. Cramer C, Ranft U, Ring J, et al. Allergic sensitization and disease in mother-child pairs from Germany: role of early childhood environment. Int Arch Allergy Immunol 2007;143:282–9.
41. Groot Kormelink T, Thio M, Blokhuis BR, Nijkamp FP, Redegeld FA. Atopic and non-atopic allergic disorders: current insights into the possible involvement of free immunoglobulin light chains. Clin Exp Allergy 2009;39:33–42.
42. Morris DL, Hersh EM, Hsi BP, Gutterman JU, Marshall MM, Mavligit GM. Recall antigen delayed-type hypersensitivity skin testing in melanoma and acute leukemia patients and their associates. Cancer Res 1979;39:219–26.
43. Advani SH, Dinshaw KA, Nair CN, et al. Immune dysfunction in non-Hodgkin's lymphoma. Cancer 1980;45:2843–8.
44. Litonjua AA, Celedon JC, Hausmann J, et al. Variation in total and specific IgE: effects of ethnicity and socioeconomic status. J Allergy Clin Immunol 2005;115:751–7.
45. Sandberg M, Frykman A, Persson M, et al. Total and allergen specific IgE antibody levels during and after pregnancy in relation to maternal allergic disease. American Academy of Allergy Asthma and Immunology Annual Meeting. San Diego; 2007.
46. Johnson CC, Ownby DR, Peterson EL. Parental history of atopic disease and concentration of cord blood IgE. Clin Exp Allergy 1996; 26:624–9.
47. Yang KD, Ou CY, Hsu TY, et al. Interaction of maternal atopy, CTLA-4 gene polymorphism and gender on antenatal immunoglobulin E production. Clin Exp Allergy 2007;37:680–7.
48. Moffatt MF, Cookson WO. The genetics of asthma. Maternal effects in atopic disease. Clin Exp Allergy 1998;28 Suppl 1:56–61; discussion 5–6.
49. Starr JR, Hsu L, Schwartz SM. Assessing maternal genetic associations: a comparison of the log-linear approach to case-parent triad data and a case-control approach. Epidemiology 2005;16:294–303.
50. Skogstrand K, Thorsen P, Norgaard-Pedersen B, Schendel DE, Sorensen LC, Hougaard DM. Simultaneous measurement of 25 inflammatory markers and neurotrophins in neonatal dried blood spots by immunoassay with xMAP technology. Clin Chem 2005;51:1854–66.
51. Skogstrand K, Hougaard DM, Schendel DE, Bent NP, Svaerke C, Thorsen P. Association of preterm birth with sustained postnatal inflammatory response. Obstet Gynecol 2008;111:1118–28.
52. Eising S, Svensson J, Skogstrand K, et al. Type 1 diabetes risk analysis on dried blood spot samples from population-based newborns: design and feasibility of an unselected case-control study. Paediatr Perinat Epidemiol 2007;21:507–17.