

Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States)

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Abstract

Objectives: To test the hypothesis that childhood acute lymphoblastic leukemia (ALL) is associated with allergic disorders.

Methods: We compared the histories of selected allergic disorders (asthma, hay fever, food or drug allergies, eczema, and hives) of 1842 cases of ALL with those of 1986 individually matched controls. The histories of the allergic disorders among siblings of cases and controls were also compared.

Results: The combined history of any one or more of the five allergic disorders evaluated was associated with a significant reduced risk of ALL (adjusted OR = 0.7, 95% CI 0.6–0.8), as were histories of four specific allergic disorders (asthma, hay fever, food or drug allergies, and eczema). The combined history of any one or more of the five allergic disorders among any of the siblings of the study subjects also revealed a significantly inverse association (adjusted OR = 0.9, 95% CI 0.8–1.0).

Conclusion: The results from this study, in agreement with most previous studies on adult cancer, suggest that allergic disorders may be associated with a reduced risk of childhood ALL.

Introduction

Two contradictory hypotheses have been proposed concerning the relationship between allergic disorders and cancers, including leukemia. The immune surveillance hypothesis, postulated by Thomas and Burnet [1, 2], suggests that allergic disorders are protective against the occurrence of cancers because an enhanced immune system can detect and destroy malignant mutant cells [3]. Most epidemiologic evidence accumulated in the past 40 years seems to support this “hyperimmune” theory of allergic response [3–10]. Alternatively, it has been suggested that immune-stimulating conditions (including infectious diseases, allergies, and autoimmune

diseases) increase the risk of cancers through a mechanism of chronic stimulation of cells that results in the occurrence of random mutations in actively dividing stem cells. This antigenic stimulation hypothesis has also been supported by some epidemiologic studies [11–13].

The complexity and heterogeneity of the association between various allergic disorders and various cancers may be one of the reasons that there are data supporting the different hypotheses [14]. To our knowledge, the relation between childhood acute lymphoblastic leukemia (ALL) and allergic disorders has not been studied. In an effort to improve our understanding of the association between selected common allergic disorders in children and childhood ALL, we present here the first epidemiologic evidence on the association, using the data obtained from interviews of subjects’ mothers that were collected in a large-scale case–control study.

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Materials and methods

Details of this case-control study have been described elsewhere [15]. Briefly, cases were identified through the member institutions of the Children's Cancer Group (CCG) throughout the United States [16]. Cases were newly diagnosed with ALL between 1 January 1989 and 15 June 1993, were under the age of 15 at diagnosis, and lived in a home with a telephone. Controls were randomly selected using a random digit dialing methodology previously described [17] and individually matched to cases on age (within 25% of age at diagnosis of the case, with a maximum difference of ± 2 years), race (white, black, or other), and telephone area code and exchange. In a few situations where an exact match could not be achieved after dialing 300 random numbers, relaxation of the age- and race-match was implemented. The control to case ratio was generally 1:1, except for the rare T-cell ALL subgroup, where more than one control was matched to each case. Additional eligibility criteria included the availability of an English-speaking biological mother for an interview.

A standard panel of monoclonal antibodies was applied to all diagnostic bone marrow specimens to determine B- or T-lineage. A subset of B-lineage leukemias was further classified by the determination of cytoplasmic immunoglobulin. Cases were assigned to one of the following mutually exclusive groups: T-cell ALL, early pre-B ALL (B-lineage markers positive, cytoplasmic immunoglobulin negative), pre-B ALL (B-lineage markers positive, cytoplasmic immunoglobulin positive), B-lineage ALL-not otherwise specified (B-lineage markers positive, but cytoplasmic immunoglobulin not performed), or unclassifiable.

During the study period, 2081 eligible cases and 2597 eligible controls were identified and a telephone interview was completed for 1914 cases (92.0%) and 1987 controls (76.5%). The 167 non-participating cases included 41 (2.0%) physician refusals, 70 (3.4%) parental refusals, 18 (0.9%) lost to follow-up, and 38 (1.8%) for miscellaneous reasons. Reasons for non-participation of 610 controls were 457 (17.6%) parental refusals, 17 (0.7%) lost to follow-up, and 136 (5.2%) for miscellaneous reasons. Matched controls or case were not found for 72 out of 1914 interviewed cases or 1 out of 1987 interviewed controls, respectively, resulting in 1842 case-control sets (1842 cases, 1986 controls, 1704 sets of 1:1 match, 132 sets of 1:2 match, and 6 sets of 1:3 match).

Information regarding the subjects' and their mothers' health history, details of maternal pregnancy and birth history, childhood diseases including allergic disorders of subjects and their siblings, family medical history,

and parental occupational history was collected through a telephone interview of mothers of study subjects using structured questionnaires. Included in the current analysis were data on allergic disorders of the subjects and their siblings and data on potential confounding factors.

Conditional logistic regression models were used in data analyses to obtain odds ratios (OR) and their 95% confidence intervals (CI). Crude odds ratios were first estimated and then ORs were adjusted for potential

Table 1. Characteristics of cases and controls

	Cases (n)	Controls (n)	OR	95% CI
Sex				
Male	1018	1076	1.0	
Female	824	910	1.0	0.8-1.1
Race				
White	1492	1720	1.0	
Other	350	266	2.6	1.9-3.5
Maternal education				
\leq High school	797	762	1.0	
Some post-high school	592	701	0.8	0.7-0.9
\geq College	453	523	0.8	0.7-0.9
Maternal age (years)				
< 25	637	646	1.0	
25-29	649	728	0.9	0.8-1.0
30-34	408	470	0.9	0.8-1.0
≥ 35	148	142	1.0	0.8-1.3
Income				
$< \$20,000$	607	546	1.0	
$\$20,000-\$39,999$	767	844	0.8	0.7-0.9
$\geq \$40,000$	468	596	0.6	0.5-0.8
Ever breastfed				
No	907	874	1.0	
≤ 6 months	533	604	0.8	0.7-1.0
> 6 months	401	508	0.7	0.6-0.9
Maternal smoked during pregnancy				
No	1300	1429	1.0	
Yes	542	557	1.1	0.9-1.2
Maternal drank during pregnancy				
No	1074	1159	1.0	
Yes	768	827	1.0	0.9-1.2
Age at diagnosis (years)				%
0-1	187			10.2
2-5	1030			55.9
6-10	409			22.2
11+	216			11.7
Immunophenotype				
T-cell	183			9.9
Early pre-B	893			48.5
Pre-B	233			12.6
B not specified	231			12.5
Unknown	302			16.4

confounders in multivariate models. Linear trend of the association was evaluated by treating the categorical variables as continuous in the models.

Results

As typical for ALL, cases were predominantly between the ages of 2 and 5 years (55.9%). Controls were more likely to be white, to come from a family with a higher maternal education level and family income, and to be breastfed more often than cases. These demographic characteristics, along with breastfed history, because of its potential relation with both ALL and allergic disorders, were controlled for their potential confounding effect. Subjects' sex, maternal age, maternal smoking and drinking during pregnancy were not significantly

associated with the risk of ALL, nor did they significantly change allergy-associated odds ratios. We found no other major confounders (Table 1).

Allergic disorders included in this analysis were asthma, hay fever, food or drug allergies, eczema, and hives. As shown in Table 2, after adjusting for breastfeeding, maternal education, family income and race, the combined history of any one or more of the five allergic disorders evaluated was associated with a significant reduced risk of ALL (adjusted OR = 0.7, 95% CI 0.6–0.8), as were histories of four specific allergic disorders (asthma, hay fever, food or drug allergies, and eczema). History of hives was associated with a nonsignificant reduced risk for ALL. The risk of ALL decreased further if a child suffered two or more allergic disorders (trend $p = 0.03$). Reduced risk of ALL was observed for all age groups (Table 2), and for

Table 2. Allergic disorders of study subjects and childhood ALL, by age at diagnosis

Allergic disorders	Number of affected subjects	Age at diagnosis (years)			
		0–1	2–5	6–10	11+
Asthma					
Case no. ¹	135	7	66	41	21
Ctrl no. ¹	176	10	89	49	28
OR (95% CI) ²	0.8 (0.6–1.0)	0.6 (0.2–1.7)	0.7 (0.5–1.1)	0.9 (0.5–1.4)	0.7 (0.3–1.3)
Hay fever					
Case no.	86	6	30	27	23
Ctrl no.	150	5	60	52	33
OR (95% CI)	0.6 (0.5–0.8)	1.2 (0.3–4.7)	0.5 (0.3–0.9)	0.5 (0.3–0.8)	0.7 (0.4–1.4)
Food and drug allergies					
Case no.	327	27	140	103	57
Ctrl no.	487	40	226	133	88
OR (95% CI)	0.7 (0.6–0.8)	0.8 (0.4–1.4)	0.6 (0.5–0.8)	0.7 (0.5–1.0)	0.6 (0.4–0.9)
Eczema					
Case no.	91	2	58	19	12
Ctrl no.	145	13	79	37	16
OR (95% CI)	0.7 (0.5–0.9)	0.1 (0.0–0.6)	0.8 (0.6–1.2)	0.5 (0.3–1.0)	0.9 (0.4–2.3)
Hives					
Case no.	136	4	65	44	23
Ctrl no.	166	11	87	39	29
OR (95% CI)	0.9 (0.7–1.2)	0.3 (0.1–1.1)	0.9 (0.6–1.2)	1.3 (0.8–2.0)	0.8 (0.4–1.5)
Any above conditions					
Case no.	545	35	267	160	83
Ctrl no.	746	59	383	187	117
OR (95% CI)	0.7 (0.6–0.8)	0.6 (0.3–0.9)	0.7 (0.5–0.8)	0.9 (0.6–1.1)	0.6 (0.4–0.9)
No. suffered from any above disorders [OR (95% CI)]					
One condition	0.8 (0.7–0.9)	0.6 (0.4–1.1)	0.7 (0.6–0.9)	1.1 (0.8–1.5)	0.6 (0.4–1.0)
Two or more	0.6 (0.5–0.7)	0.4 (0.1–0.9)	0.6 (0.4–0.8)	0.6 (0.4–0.9)	0.6 (0.3–0.9)
Trend p	0.03	0.72	0.35	0.02	0.97

¹ Case no.: the number of cases with allergic disorder; Ctrl no.: the number of controls with allergic disorder.

² Odds ratios were adjusted for months of breastfeeding, maternal education, race, and family income. Tests for trend were assessed in logistic models containing a given factor as ordinal instead of as a set of indicator variables.

all immunophenotypes of the ALL cases (data not shown), although not all risk estimates were statistically significant.

In general, risk of ALL was reduced among children who had at least one sibling with one of the five specific allergic conditions. As presented in Table 3, the combined history of any one or more of the five allergic disorders among any of the siblings of the study subjects revealed a significant inverse association (adjusted OR = 0.9, 95% CI 0.8–1.0), although the OR estimate was significant only for specific history of hay fever (adjusted OR = 0.7, 95% CI 0.6–0.9) and food and drug allergies (adjusted OR = 0.8, 95% CI 0.7–1.0). Having three or more siblings affected might have the lowest risk of ALL (adjusted OR = 0.7, 95% CI 0.5–0.9), but no significant dose–response relationship was found (trend $p = 0.44$). All the analyses were adjusted for number of siblings, breastfeeding, maternal education, family income and race.

Discussion

The results from our study, in agreement with most previous studies on adult cancers [3–10], suggest that allergic disorders may be associated with a reduced risk of childhood ALL. Despite the current controversial status of the immune surveillance hypothesis, it has been observed that children with various congenital immunodeficiency diseases have an increased risk of developing lymphoid malignancies [18–20]. Abnormalities of the immune system are occasionally observed in patients newly diagnosed with ALL, but it is unclear whether these abnormalities precede the development of leukemia or are a consequence [18–20]. Our study cannot determine the time sequence of the relationship between allergic disorders and ALL because of the lack of information on the age at onset of allergic disorders. However, we found an inverse association between risk of ALL and eczema, an allergic disorder that usually occurs in infancy in our study, not only among infants but also among older children. This inverse association suggests that the less frequent allergic disorders in case children are unlikely to be a consequence of leukemia. In addition, we observed that some allergic disorders among the subjects' siblings, with whom the subjects may share genetic and environmental determinants of allergic disorders [21], were also associated with a reduced risk of ALL (Table 3). A 4-fold excess risk of childhood leukemia was estimated among siblings of ALL cases in one study [22]. Likewise, many serious allergic conditions have been determined to have a familial and genetic basis [21]. Thus, it is possible that an underlying familial or genetic basis may be responsible for

Table 3. Allergic disorders among subjects' siblings and childhood ALL

Allergic disorders	Cases	Controls	OR ¹	95% CI
Asthma				
Any sibling with condition	157	188	1.0	0.8–1.2
No. of siblings suffered				
1	135	167	0.9	0.7–1.2
2+	22	21	1.1	0.6–2.1
Trend p				0.58
Hay fever				
Any sibling with condition	141	215	0.7	0.6–0.9
No. of siblings suffered				
1	113	175	0.7	0.5–0.8
2+	28	40	0.8	0.4–1.3
Trend p				0.48
Food and drug allergies				
Any sibling with condition	362	476	0.8	0.7–1.0
No. of siblings suffered				
1	304	387	0.8	0.7–0.9
2+	58	89	0.8	0.5–1.1
Trend p				0.40
Eczema				
Any sibling with condition	114	141	0.9	0.7–1.2
No. of siblings suffered				
1	103	124	1.0	0.7–1.3
2+	11	17	0.8	0.4–1.7
Trend p				0.23
Hives				
Any sibling with condition	126	144	1.0	0.8–1.2
No. of siblings suffered				
1	114	127	1.0	0.8–1.3
2+	12	17	0.7	0.3–1.6
Trend p				0.65
Any above disorders				
Any sibling with condition	570	705	0.9	0.8–1.0
No. of siblings suffered				
1	303	346	0.9	0.8–1.1
2	155	182	0.8	0.6–1.1
3+	112	177	0.7	0.5–0.9
Trend p				0.44

¹ Odds ratios were adjusted for the number of siblings, breastfeeding, maternal education, race, and family income.

the reduced risk of childhood ALL among children with certain types of allergic disorders. We conclude that our data support the immune surveillance hypothesis and suggest that the genetic and/or environmental factors that cause allergic disorders may also be protective against ALL. We hope that the finding reported here will

stimulate more studies, including prospective surveillance studies of carefully defined allergic disease cohorts.

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