

Invited Commentary

Invited Commentary: Childhood Acute Lymphoblastic Leukemia and Allergies: Biology or Bias?

Amy M. Linabery* and Logan G. Spector

* Correspondence to Dr. Amy M. Linabery, Department of Pediatrics, University of Minnesota, 420 Delaware Street SE, MMC 715, Minneapolis, MN 55455 (e-mail: linabery@umn.edu).

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Previous epidemiologic studies have shown an inverse association between a personal history of atopy/allergies, both overall and among asthma, eczema, and hay fever investigated separately, and childhood acute lymphoblastic leukemia (ALL) with some consistency; however, in most of these studies, exposure data were collected by maternal interview. Now, in a population-based and records-based study in this issue of the *Journal* (*Am J Epidemiol.* 2012;176(11):970–978), Chang et al. report an increased risk for allergic conditions across different etiologic time periods, calling the former paradigm into doubt. A review of the basic biology literature shows that proposed mechanisms support either a positive or an inverse association. In light of this ambiguity, it is epidemiology's turn to determine the direction of association.

child; hypersensitivity; leukemia

Abbreviations: ALL, acute lymphoblastic leukemia; IgE, immunoglobulin E; IL, interleukin; NCCLS, Northern California Childhood Leukemia Study; Th2, type 2 helper T; TNF- α , tumor necrosis factor alpha; UKCCS, United Kingdom Childhood Cancer Study.

Determining a causal association between exposure and disease is an iterative process between epidemiology and basic science. If only every iteration brought us closer to the truth, we could all rest easy; however, in actuality, the process seems more akin to a random walk. Case in point: With the publication by Chang et al. in this issue of the *Journal* (1), what appeared to be a consistent inverse association between allergies and childhood acute lymphoblastic leukemia (ALL) is now being called into question.

In a recent meta-analysis of the topic, Linabery et al. examined 8 case-control studies of ALL that met the search criteria (2). The odds of allergy were significantly lower in ALL cases than in controls (odds ratio = 0.69; 95% confidence interval: 0.54, 0.89), and similarly inverse associations were observed for asthma, eczema, and hay fever analyzed separately. These associations varied across studies stratified by a number of factors that could potentially influence outcome, however, including those related to study design and response rates. Importantly, odds ratios were null for 3 studies in which allergy information was

obtained from medical records rather than from maternal report and investigators accounted for a latent period before ALL diagnosis.

This somewhat contrarian research consisted of a case-control study nested within the populations of 4 United States health maintenance organizations, the United Kingdom Childhood Cancer Study (UKCCS), and a Swedish record-linkage study of hospital discharge for asthma. In the first study, the odds ratio for allergies was elevated at 1.24 but was imprecisely estimated (95% confidence interval: 0.82, 1.86) (3), whereas in the second and third studies, point estimates were inverse at 0.87 (95% confidence interval: 0.72, 1.06) (4) and 0.5 (95% confidence interval: 0.2, 1.1) (2, 5) but also not significant. Although all 3 studies relied on medical records for exposure assessment, the US and Swedish studies were entirely record-based and in this respect were the most similar to the present study, whereas the UKCCS required active participation.

Chang et al. conducted a population-based and registry-based study through the linkage of several comprehensive

data sets within the National Health Insurance Research Database of Taiwan (1). They reported control prevalences of 11%–16% for allergic conditions occurring more than 1 year before the diagnosis date, which is in line with prevalences described in the United States and in other pediatric populations (6–8). They found a slight but statistically significantly increased risk for childhood ALL in children with a prior history of allergies occurring before 1 year of age, less than 1 year before ALL diagnosis, and more than 1 year before ALL diagnosis. Positive associations were observed for increasing number of allergic conditions (≥ 3) occurring both less than 1 year and more than 1 year before ALL diagnosis, as well as for allergic rhinitis, asthma, atopic dermatitis, and urticaria examined individually.

An important consideration in interpreting this body of literature is the difficulty in accurately assessing allergic status. Many studies have relied upon parental report (9–13), which is subject to selection and recall bias, as well as misclassification. As mentioned above, others have assessed allergic status using medical records (1, 3–5), which are often considered the gold standard for medical history data but which may not be complete for allergic diseases. Therefore, misclassification of allergic status can result from either source because allergies may not be identified by parents or physicians. In support of this supposition is the estimate that 30%–40% of “healthy” individuals are actually atopic (14). In addition, symptoms in allergic individuals can both increase and decrease over time (15). Missing and misclassified data in medical records tend to be nondifferential (although only in likelihood (16)). By comparison, one would presume some degree of differential misclassification introduced by parental recall. We speculate that mothers of controls may be more likely to report a history of allergies than mothers of cases because of case parents forgetting or minimizing the importance of other health conditions in the presence of malignancy or waning of allergic response as part of an ALL prodrome. Given these challenges, perhaps it is not surprising that somewhat conflicting results have been presented.

The manner in which parents are asked about their children’s allergy histories may contribute to the quality of information returned. For instance, in 2 studies, investigators specifically asked parents to recall allergic conditions diagnosed by physicians, which at least in theory should elicit the same conditions one would obtain from medical records (10, 11). Three other studies did not specify how the question was asked, leaving the possibility that investigators solicited a broader array or severity of conditions (9, 12, 13). Regardless of how the question is asked, parents’ responses depend on their understanding of what counts as an allergic condition, as well as their awareness of allergic symptoms. For example, food or drug intolerance that operates through nonimmune mechanisms may nevertheless be understood by parents to qualify as allergies (17). Further, medical records permit abstraction of exact timing and ordering of events, whereas parental recall would not be expected to be as precise.

Validation studies comparing parental report and medical records have shown greater agreement regarding asthma diagnosis (with 87% agreement (18) in one study and 88% in

another (19)) but less agreement with respect to other allergic conditions (39% agreement for hay fever, eczema, or urticaria (19)). Similarly, a validation study comparing maternal report of physician-diagnosed eczema to examination by a dermatologist found modest agreement ($\kappa = 0.34$) (20). In the UKCCS investigation, Hughes et al. reported high maternal recall of asthma in both cases and controls (sensitivity_{cases} = 81% vs. sensitivity_{controls} = 83%), although case mothers showed somewhat better agreement with medical records ($\kappa_{cases} = 0.69$ vs. $\kappa_{controls} = 0.60$) (4). Eczema was reported less frequently (sensitivity_{cases} = 51% vs. sensitivity_{controls} = 57%), but case and control mothers had equal agreement with medical records ($\kappa = 0.46$). On the basis of these results, case and control parents would be expected to display similar recall for a given allergic condition, and different levels of recall would be expected across the individual conditions.

On balance, the methodology favors the results of the record-based studies that were assured proper temporality and permitted analysis of different latency periods while eliminating the opportunity for recall or selection bias. Does the biology also support a positive association of ALL and allergies? The evidence is, unfortunately, equivocal.

A number of plausible mechanisms have been proposed to support both positive and inverse associations between allergic diseases and malignancy. Atopic diseases/allergies involve an exaggerated (type 1) hypersensitivity reaction to an allergen resulting in antigen presentation, increased serum immunoglobulin E (IgE) antibody concentrations, increased levels of CD4+ type 2 helper T (Th2) cell-associated cytokines, and recruitment and activation of leukocytes, leading to inflammation (21, 22). In support of a positive association is the antigen stimulation theory, which holds that the immune systems of atopic individuals are perpetually stimulated by allergens, resulting in chronic inflammation and stimulation of cell proliferation (23). On the basis of results of epidemiologic, genetic, and molecular biology studies, a causal relation between inflammation and malignancy is widely accepted, although the mechanisms are still under investigation (24). A greater rate of cell growth and reduced apoptosis may increase the opportunity for genetic errors to accumulate and propagate, resulting in increased risk for malignancy (23). A Th2-dominated immune profile may promote leukemia by promoting angiogenesis in the bone marrow (by eosinophils, mast cells, macrophages, and plasma cell-derived immunoglobulin G immune complexes), by inhibiting apoptosis (by interleukin (IL)-4 and IL-6), and/or by suppressing antigen presentation by antigen-presenting cells and tumor cell elimination by CD8+ cytotoxic T lymphocytes (by IL-10, by IL-13-stimulated release of transforming growth factor β and suppression of interferon gamma and by immune complexes) (22, 25–27). There is research suggesting that soluble CD23 (a fragment of the IgE receptor that acts as a cytokine) and chemokines produced by type 17 helper T cells also foster development of B-cell ALL by inhibiting apoptosis (28, 29).

On the other hand, the immune surveillance theory (or, more properly, the prophylaxis theory (23)) has been

invoked to explain observed inverse associations between allergy and malignancy. This hypothesis purports that atopy may increase the vigilance of an individual's immune system in the recognition and eradication of pathogens and other foreign bodies, including cancer cells (23). The exact human biology underlying it has not been established, but there is evidence supporting antitumor immunity mediated by CD4⁺ Th2 cells specific for a given tumor antigen (reviewed in references 22 and 25). Release of Th2 cytokines recruits and activates eosinophils, macrophages, type 2 CD8⁺ T cells, and natural killer cells, which participate in tumor surveillance and mount antitumor attacks. Th2 cytokines perform other relevant functions as well. For example, tumor necrosis factor α has direct antitumor cytotoxic effects, IL-4 may inhibit angiogenesis, and IL-10 reduces expression of inflammatory cytokines and directly inhibits inflammation-associated carcinogenesis (22, 25, 26). Elevated levels of IgE in atopic individuals is thought to enhance these immunosurveillance and tumoricidal effects through tight binding to its high-affinity receptors expressed on multiple cell types, as well as binding to receptors for other immunoglobulins (e.g., immunoglobulin G) on additional cell types (22). Other proposed pathways include 1) diminished B-cell response resulting from IgE binding to its lower-affinity receptor (CD23) and preventing release of soluble CD23 and 2) reduced type 17 helper T cell cytokine secretion in persons with atopy (22).

The difficulty in uncovering the mechanism(s) linking allergy and cancer lies in the pleiotropic functions of several immune cells and mediators, such as eosinophils, IL-4, and IL-10, in different contexts (22, 27). It is conceivable that different mechanisms may be applicable to different cancers depending on the tissue of origin, the microenvironment, and/or presence of other necessary activating signals (22, 27). The immune surveillance theory has been most often cited with respect to childhood ALL, but that theory followed observations that have now been called into doubt.

Reverse causality is another potential consideration, but seems unlikely for 2 reasons. First, ALL might be predicted to cause atopic symptoms to wane in intensity, as has been observed for non-Hodgkin lymphoma patients (30, 31). This would result in an inverse association, whereas Chang et al. (1) and Spector et al. (3) found increasing odds of allergy closer to the date of ALL diagnosis. Further, reverse causality is a less-convincing explanation for associations seen over a longer latency period, such as those observed by Chang et al. (1).

Ultimately, this association needs to be explored in multiple avenues beyond medical records and parental report. Prospective biomarker studies would be ideal, if robust biomarkers specific to allergic conditions could be identified and measured in a large enough group of children, although this would be challenging given the rarity of ALL. The Northern California Childhood Leukemia Study (NCCLS) neonatal dried blood spot analysis showing decreased levels of IL-10 in ALL cases compared with matched controls provides an elegant example (32). The NCCLS article showing a positive association between maternal serum IgE levels and childhood ALL is another example, although the

cross-sectional study design did not permit proper temporality (33). Another potential approach is the assessment of eosinophil levels in whole blood (34). The International Childhood Cancer Cohort Consortium, which has the goal of recruiting 1 million children, may provide the needed sample size and biospecimens to facilitate such research (35, 36).

Genetic susceptibility studies provide a further possible direction. Results of twin and other family-based studies indicate a substantial genetic component to allergic diseases (37, 38). In their study of immune response genes and childhood ALL, NCCLS investigators found significant associations with 19 single nucleotide polymorphisms; however, only 1 single nucleotide polymorphism in the interleukin 12A gene remained significant after correction for multiple testing (39). As additional genome-wide studies become available regarding common variation conferring susceptibility to allergic diseases across different populations (40–42), it may be worthwhile to consider these candidate variants for investigation in ALL.

In summary, although atopic disease and childhood ALL appear to have some sort of relation to each other, the nature and direction of the association is as yet undetermined. Although we might hope that biology would contribute some clarity, the immune system is complex, context-dependent, and ambiguous in this regard. Thus, it is up to epidemiology to ensure that the next iteration of studies is an innovative one, in which allergic status is accurately assessed (2, 4, 11, 31–33) before the development of childhood ALL, and not simply a reiteration (“to state or do over again or repeatedly sometimes with wearying effect”) of past study designs.

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Author affiliations: Division of Pediatric Epidemiology and Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota (Amy M. Linabery, Logan G. Spector); and University of Minnesota Masonic Cancer Center, Minneapolis, Minnesota (Logan G. Spector).

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