

Response to Invited Commentary

Chang et al. Respond to “Allergies and ALL: Biology or Bias?”

Jeffrey S. Chang*, Yi-Wen Tsai, Chia-Rung Tsai, and Joseph L. Wiemels

* Correspondence to Dr. Jeffrey S. Chang, 1F No 367, Sheng-Li Road, Tainan 70456, Taiwan, Republic of China (e-mail: jeffreychang@nhri.org.tw).

Initially submitted April 30, 2012; accepted for publication May 11, 2012.

Abbreviation: ALL, acute lymphoblastic leukemia.

We thank Drs. Linabery and Spector for their commentary (1) on our analysis of the association between allergies and childhood acute lymphoblastic leukemia (ALL) (2). We appreciate their thorough presentation of the potential biases that may occur in epidemiologic studies examining the association between allergies and childhood leukemia, possible biologic mechanisms linking allergies to childhood leukemia, and suggestions for future research.

In a case-control study, it is always a challenge to obtain an accurate exposure history, especially in studies that rely on self-reported data. As noted by Linabery and Spector, children's histories of allergies supplied via parental reports can be subject to selection and recall biases and misclassification. Although information on allergies obtained from medical records is less likely to be subject to differential misclassification due to the differential recall between case and control parents, these data only include symptomatic individuals who visit medical facilities for treatment. Given these limitations, studies may need to incorporate data on molecular biomarkers, such as genetic polymorphisms, serum immunoglobulin E, and cytokine profiles, to investigate the relation between allergies and childhood leukemia.

Genetic polymorphisms may serve as valuable markers to help disentangle the relation between allergies and childhood leukemia because they are present before the development of childhood leukemia, not subject to recall bias, and not affected by confounding because of their random inheritance from the parents (3). In a recent study, Miedema et al. examined the association between polymorphisms of several toll-like receptor genes, key components of innate immunity, and childhood ALL or atopic disease (4). The authors reported that the association between 2 single nucleotide polymorphisms of toll-like receptor 6 (rs5743798 and rs6531666) and childhood ALL and the association between the 2 single nucleotide polymorphisms and atopic

disease were in the opposite direction, supporting the role of the immune surveillance hypothesis in the inverse association between atopic disease and childhood ALL (4). More studies need to be conducted to confirm the finding of that study. In addition, because allergy is a complex disease likely involving the interplay between many genes, a more comprehensive survey of the polymorphisms of the immune function genes is necessary.

In addition to genetic polymorphisms, serum markers such as immunoglobulin E and cytokines may be used as more objective measures of allergies to investigate the relation between allergies and childhood leukemia (5, 6). Along with allergy, an extension to other measures of immune stimulation and/or repression (e.g., measures of infection and infection severity and T-cell subsets such as T-regulatory cells) will help to assess in a comprehensive fashion immune status and leukemia risk. The timing of the biomarker assessment is critical because measurements taken close to the time of childhood leukemia diagnosis may suffer from reverse causality. Archived newborn blood spots from congenital disease screening programs are a valuable source of data for the investigation of the atopic tendency of a child and his/her later development of childhood leukemia. However, archived newborn blood spots represent only a snapshot of the children's allergy status, which is dynamic and can develop or disappear anytime during childhood. Therefore, a longitudinal design with multiple measurements at various time points may be more ideal in tracking the relation between allergies and childhood leukemia. This may only be achieved by a large cohort, such as the International Childhood Cancer Cohort Consortium (7), given the rare occurrence of childhood leukemia.

In conclusion, case-control studies of childhood leukemia based on parental report or medical records for obtaining the children's history of allergies may have reached

their limit. In future studies, investigators need to consider alternative study designs and incorporate various molecular biomarkers to help clarify the relation between allergies and childhood leukemia.

ACKNOWLEDGMENTS

Author affiliations: National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan (Jeffrey S. Chang, Chia-Rung Tsai); Institute of Health and Welfare Policy, National Yang-Ming University, Taipei, Taiwan (Yi-Wen Tsai); and Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California (Joseph L. Wiemels).

Dr. Jeffrey S. Chang was supported by the National Science Council of Taiwan (grant NSC 99-2314-B-400-004) and the Department of Health, Taiwan (DOH101-TD-C-111-004). Dr. Joseph L. Wiemels was supported by the Leukemia and Lymphoma Society of America (grant 6026-10).

Conflict of interest: none declared.

REFERENCES

1. Linabery AM, Spector LG. Invited commentary: childhood acute lymphoblastic leukemia and allergies: biology of bias? *Am J Epidemiol.* 2012;176(11):979–983.
2. Chang JS, Tsai YW, Tsai CR, et al. Allergy and risk of childhood acute lymphoblastic leukemia: a population-based and record-based study. *Am J Epidemiol.* 2012;176(11):970–978.
3. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol.* 2004;33(1):30–42.
4. Miedema KG, Tissing WJ, Te Poele EM, et al. Polymorphisms in the TLR6 gene associated with the inverse association between childhood acute lymphoblastic leukemia and atopic disease. *Leukemia.* 2012;26(6):1203–1210.
5. Chang JS, Buffler PA, Metayer C, et al. Maternal immunoglobulin E and childhood leukemia. *Cancer Epidemiol Biomarkers Prev.* 2009;18(8):2221–2227.
6. Chang JS, Zhou M, Buffler PA, et al. Profound deficit of IL10 at birth in children who develop childhood acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev.* 2011;20(8):1736–1740.
7. Brown RC, Dwyer T, Kasten C, et al. Cohort profile: the International Childhood Cancer Cohort Consortium (I4C). *Int J Epidemiol.* 2007;36(4):724–730.