In the latest report from the United Kingdom Childhood Cancer Study (UKCCS), Roman et al. (1) describe an association between early-onset childhood acute lymphoblastic leukemia (ALL) and increased early infections. This study is a welcome development, following the studies that used proxy measures for infectious exposure (2). Roman et al. concede that the results do not support Greaves’ delayed infection hypothesis (3) but conclude that they point towards an abnormal immune response to infection (1). We believe there may be alternative explanations.

One hypothesis the UKCCS was launched to test was that the development of ALL is related to “abnormal responses to common infectious agents” triggered by “paucity of infectious exposure in infancy” (4, p. 1074). Many studies, including another UKCCS study (5), have seemed to support a pattern of reduced exposure to infections preceding the development of childhood leukemia. Roman et al. (1) directly investigated observed episodes of infection, and the results are inconsistent with previous studies. They conclude that their findings “support the hypothesis that a dysregulated immune response to infection in the first few months of life promotes transition to overt ALL” (1, p. 496). However, the original hypothesis predicted an abnormal response by an immune system that remained immature due to lack of infectious exposures early in life; the hypothesis has been reiterated more recently (6).

Abnormal immune response has been speculated about but not observed in childhood ALL. Data generated from studies using proxy measures for exposure or observations of population mixing and space-time clustering (2, 6, 7) have valid alternative explanations. In support of an abnormal immune response, now purported to be triggered by a surfeit rather than a deficit of early infections, Roman et al. cite another UKCCS study (17), particularly in infancy (18), the observed association should be stronger among boys (as is the HLA-DR association (11, 12)). However, results of sex-specific analyses were not presented by Roman et al. (1).

These alternative explanations of the UKCCS data should also be considered. Instead of invoking an abnormal immune response, we favor the explanation that subtle immunodeficiency results in increased infections as well as increased ALL risk.

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REFERENCES


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