CORRESPONDENCE

Re: Childhood Leukemia Incidence in Britain, 1974–2000: Time Trends and Possible Relation to Influenza Epidemics

Kroll et al. (1) recently reported incidence time trends for childhood leukemia in Britain during 1974–2000 and suggested that small peaks in incidence may be associated with influenza epidemics. The authors observed an overall increase in childhood leukemia during this period that they attributed to precursor B-cell subtype of acute lymphoblastic leukemia (ALL). This finding is largely confirmatory of a previous, albeit smaller, study from Northwest England (2).

A number of previous epidemiologic studies have suggested that infectious disease may be involved in the etiology of childhood leukemia, and other studies have found that, as would be expected from such an etiology, cases of childhood leukemia display a propensity to cluster in space and time (3,4). Such an unusual pattern suggests that the putative infections occur in “mini-epidemics.” By contrast, ubiquitous or endemic infections would not be predicted to lead to such space–time clustering. Our studies from Northwest England found that space–time clustering was limited to leukemia of precursor B-cell subtype (5). This observation provides additional evidence that epidemic infections may be involved with this subtype specifically. Finally, cyclical, epidemic-like patterns in the magnitude of the space–time clustering for childhood ALL have been observed (6), which suggests the involvement of one or more common infections in etiology.

There are a number of apparent limitations to the study by Kroll et al. (1). One is that it is not clear why the authors focused on influenza in particular. Several of other infectious agents, including measles, chicken pox, and adenovirus, are equally plausible candidates for an association with leukemia. The authors’ suggestion that incidence peaks are linked to influenza appears to be based entirely on the observation that two small peaks in incidence of ALL occurred in the 2 years immediately following influenza epidemics. Although the authors note that the coincidence of two small peaks in ALL with influenza may be attributable to chance, they made no formal attempt to assess the statistical significance of this observation. Moreover, the proportion of extra ALL cases that occurred in the peak years that immediately followed the influenza epidemics is far less than the proportion of extra influenza cases. Thus, if influenza is involved in the etiology of childhood ALL, it must be involved for only a limited number of individuals. A large case–control study from the United Kingdom has suggested that infections may be involved in cases of ALL in patients who have a particular pattern of immune response genes (7). A more plausible hypothesis than the one of Kroll et al. is that it is the individual’s response to infection rather than any specific infection that precipitates leukemia, but certain infections are more likely to stimulate a cytokine-driven proliferation. Finally, Kroll et al. analyzed data based on the time of diagnosis. However, an infection occurring in utero or around the time of birth would be predicted to generate an epidemic pattern based on time of birth, rather than time of diagnosis.

More research is needed to enhance understanding of the role that infections, including influenza, may play in the etiology of childhood ALL. Further studies on immune response genes as well as linkage to infectious disease patterns are required. Ultimately, such studies should lead to better understanding of leukemia etiology.

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RESPONSE

We thank Dr McNally and Professor Eden for comments on our recent paper, which reported time trends in subtypes of childhood leukemia in Britain during 1974–2000 and noted the coincidence of small peaks in incidence of acute lymphoblastic leukemia (ALL) with epidemics of influenza (1). We agree that the national time trend for B-precursor ALL is consistent with one of two previous regional studies (2,3) covering about 13% and 9% of the national population, respectively. We are grateful for this opportunity to amplify some points concerning influenza.

We chose to focus on influenza because it is caused by an unstable virus that mutates frequently: an epidemic represents the emergence of a new strain to which there is little existing herd immunity. Most adults in Britain have at least partial immunity to other common infections, such as measles, chicken pox and adenovirus. Lack of herd immunity is part of the mechanism proposed in Kinlen’s hypothesis (4) and may be related to the mechanism of Greaves’ hypothesis (5).
We agree, and said, that the association may be due to chance. It is impossible to conduct a valid significance test because the observation was made after the leukemia data had been analyzed, without a well-defined prior hypothesis.

The association is consistent with either a nonspecific effect of infection or a specific effect of influenza (or particular strains of influenza or some unknown secondary infection), combined with lack of immunity in the adults around the child and perhaps other factors. The proportionate increase in ALL was less than the proportionate increase in influenza. McNally and Eden say that this means that influenza can be involved for “only a limited number of individuals.” Even a limited association could be important. However, it is not clear that either Kinlen’s or Greaves’ hypothesis would predict a simple dose–response effect because both involve immunity as well as infection. The weekly all-ages consultation rate for “flu and flu-like illnesses” in selected general practices is designed to identify changes in activity, not to measure infection accurately. (Many “flu-like illnesses” are not influenza. Many respiratory illnesses are not reported to a doctor. Various strains of influenza circulate each winter. Young children have frequent respiratory infections, some of which may be undiagnosed influenza.) It certainly does not measure individual variations in immune function or local variations in prevalent strains of influenza and herd immunity.

The observed “epidemic pattern” was based on the time of diagnosis of ALL, which is consistent with both Greaves’ and Kinlen’s hypotheses—not with Smith’s hypothesis (6), according to which an infection occurring in utero or around the time of birth would be predicted to generate an epidemic pattern based on time of birth.

There is considerable evidence that infection and immunity are involved in the etiology of childhood leukemia, particularly ALL. If not due to chance, this observation appears to implicate a particular infection in at least some cases and identify the time of exposure as being shortly before the diagnosis of ALL.

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