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

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Time trends in incidence of disease may cast light on etiology. We investigated time trends in childhood leukemia by using Poisson regression methods to analyze data from the National Registry of Childhood Tumours, a long-standing high-quality registry that covers the whole childhood population of Britain. During 1974–2000, the average annual percentage change in rate (AAC) of childhood acute lymphoblastic leukemia (ALL) in Britain was 0.7% (95% confidence interval [CI] = 0.4 to 1.0). This increase was apparently driven by the "common" subtype (expressing the CD10 antigen) of precursor B-cell ALL, for which the estimated AAC during 1980–1996 was 1.4% (95% CI = 0.8 to 2.0). There was no statistically significant time trend in other subtypes of ALL combined (1980–1996) or in acute myeloid leukemia (1974–2000). Small peaks in incidence of ALL in 1976 and 1990 coincided with years immediately following influenza epidemics. These results are consistent with hypotheses that some childhood leukemia may be triggered by infection occurring close to the time of diagnosis of leukemia, particularly in conditions of low herd immunity, and raise the possibility that contact with influenza shortly before the diagnosis of leukemia may sometimes be involved. [J Natl Cancer Inst 2006;98:417–20]

Childhood leukemia is a heterogeneous group of diseases that vary in clinical behavior and, probably, etiology. The largest subgroup, acute lymphoblastic leukemia (ALL), can be subdivided by immunophenotype into CD10-positive precursor B-cell ("common") ALL (cALL), which is diagnosed mostly between ages 1 and 6 years and peaks at ages 2 and 3, and several other rarer types with different age patterns. Causation is likely to be multifactorial. Two closely related hypotheses associate the risk of leukemia with infection or lack of immunity shortly before the time of diagnosis of leukemia. Greaves *(1)* has suggested that cALL results from a sequence of two "hits." The first occurs before or shortly after birth, from unknown causes. The second occurs when the immune system is challenged by common infections, particularly in children who were unusually well protected from infection in infancy (the "hygiene hypothesis"). Kinlen has suggested that some childhood leukemia is a rare response to unknown but specific common infection(s) *(2)*. An excess of leukemia is predicted in conditions of low herd immunity when a susceptible population is exposed to such infection for the first time by population mixing.

Analysis of disease trends over time may generate or support hypotheses concerning etiology, particularly if the population is large enough for random fluctuations to be relatively small. With the aim of investigating possible relationships between infection and immunity and the incidence of childhood leukemia, we used data from the National Registry of Childhood Tumours (NRCT) to examine trends in leukemia diagnosed in children under the age of 15 in England, Wales, and Scotland from 1974 to 2000—a total of 11 790 cases.

The NRCT is the largest specialist population-based childhood cancer registry in the world, covering Britain from 1962 onwards. Ascertainment is from multiple sources, including national and regional cancer registries, specialist registries, clinical trials registers, and death certificates. Diagnostic methods for leukemia were well established by 1974, the first year in which the proportion of leukemia cases that were not identified to any particular subtype fell below 2%.

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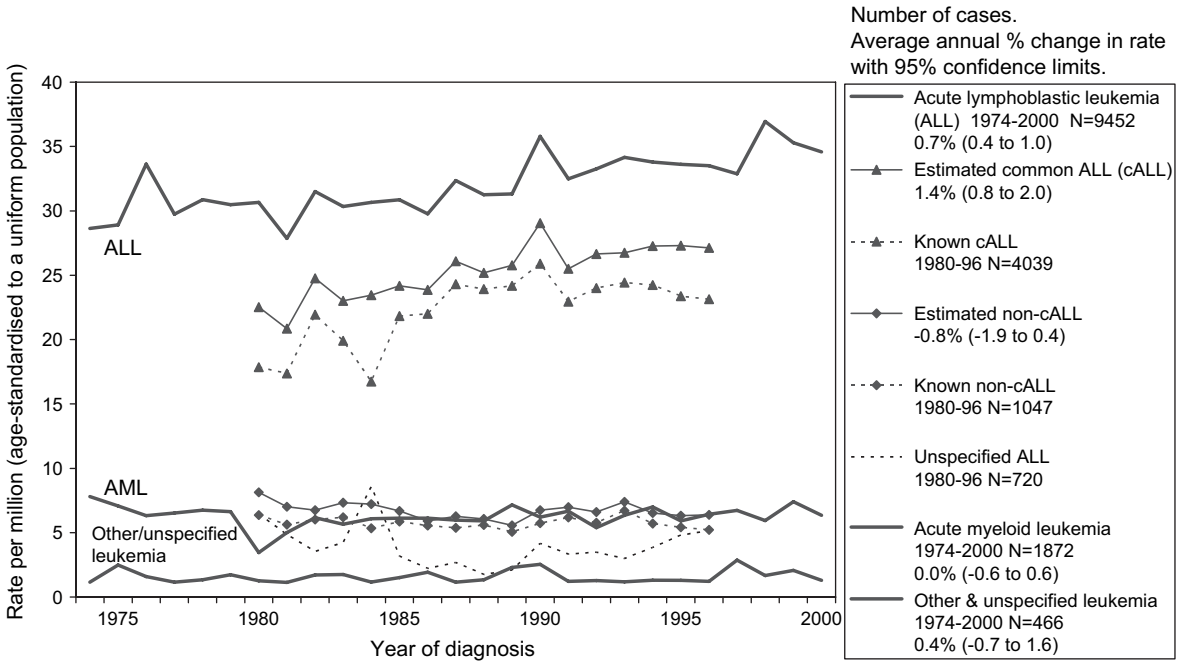

Fig. 1. Annual recorded leukemia incidence rates among children aged 0–14 years, Britain, 1974–2000.

Completeness of registration of leukemia and non-Hodgkin lymphoma in the NRCT during 1974–1983 has been estimated at 99% *(3)*. A recent comparison of the NRCT with the records collected independently for the United Kingdom Childhood Cancer Study *(4)*, a national case–control study covering periods within 1991–96, found only one apparently eligible leukemia case that had not been reported to the NRCT. It seems likely that the NRCT would have missed very few cases during the study period.

Figure 1 shows recorded annual leukemia incidence rates for 1974–2000, standardized to a uniform population by age groups 0, 1–4, 5–9, and 10–14 years. Immunophenotype information, derived mainly from national Medical Research Council clinical trials, was available for 88% of the ALL cases diagnosed during 1980–1996. We estimated the total numbers of cALL and non-cALL cases in each of these years by allocating the unspecified ALL cases in each year to the two diagnostic types according to the proportions by age group and sex of the two diagnostic types among the cases with known phenotype in that year, rounding to the nearest integer. We used log-linear modeling of Poisson rates (Stata version 8), adjusting for age group and sex, to calculate the average annual percentage changes in rate (AAC), with 95% confidence intervals (CI), over the period 1974–2000 for the main leukemia subgroups and the period 1980–1996 for the subtypes of ALL (Fig. 1).

During 1974–2000, there was a clear increasing trend in the incidence of ALL, with AAC = 0.7% (95% CI = 0.4% to 1.0%). During 1980–1996, the period for which more detailed information was available, the increase in ALL was apparently due to a specific increase in cALL, for which the estimated AAC was 1.4% (95% CI = 0.8% to 2.0%).The increase in cALL cannot be explained by changes in the classification boundary between lymphoma and leukemia, because precursor B-cell phenotypes are rare in childhood non-Hodgkin lymphoma *(5)*. Neither the increase in ALL nor the increase in cALL is likely to be due to improvements in completeness of registration, because there was no increase in acute myeloid leukemia during 1974–2000 (AAC = 0.0%, 95% CI = −0.6% to 0.6%; $P = .03$ for the two-sided test for the difference in trend between ALL and acute myeloid leukemia) or in estimated non-cALL immunophenotypes of ALL during 1980–1996 (AAC = −0.8%, 95% CI = −1.9% to 0.4%; $P = .001$ for difference in trend between estimates of cALL and non-cALL). The apparently specific increase in cALL suggests that cALL differs in etiology from other leukemias and that some contributing factor for cALL has changed over time.

Examination of Fig. 1 reveals small peaks in the ALL rate in 1976 and 1990, driven in 1990 by cALL. Each of these peaks occurred during the calendar year immediately following a winter influenza epidemic in England and Wales, as identified by the measure that was conventional for that time period: a weekly general practitioner (GP) consultation rate for influenza and influenza-like illnesses higher than 400 per 100 000 all-ages population *(6)* (Fig. 2). This coincidence may, of course, be due to other factors, or to chance; indeed, a slightly less well-defined ALL peak in 1998 followed an unusually low GP consultation rate. However, if there is a real association, it is consistent with both Greaves's and Kinlen's hypotheses. Unlike other infections that were common and well-documented in Britain during those years, influenza is caused by a family of viruses that mutate frequently; epidemics represent the emergence of newly mutated strains to which there is little existing population immunity. In the context of Greaves's hypothesis, infection with influenza would be an example of a second hit in an unprepared immune system; the general increasing trend in cALL could be the result of factors affecting the first hit, factors leading to reduced exposure of infants to infection, or both. In the context of Kinlen's hypothesis, the contact between individuals infected with a new strain of influenza and the previously unexposed population would be analogous to population mixing.

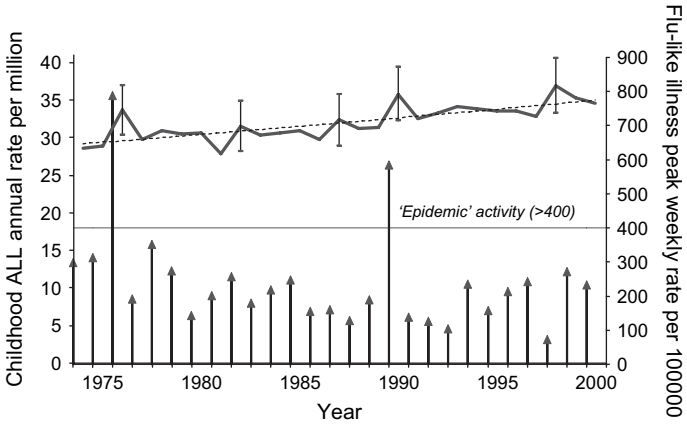

Fig. 2. Incidence of childhood acute lymphoblastic leukemia (ALL) and occurence of influenza epidemics, Britain, 1974–2000. The **line at the top** shows the annual recorded incidence rate of ALL in children aged 0–14 years, age-standardized to a uniform population, with the fitted trend line (**dashed line**) and 95% confidence intervals for the peaks (**error bars**). The **vertical arrows** show the peak weekly general practitioner consultation rate for influenza and influenza-like illnesses per 100 000 population, all ages, in sentinel practices in England and Wales during the preceding winter. "Epidemic" influenza activity was defined as a consultation rate greater than 400.

Many studies, reviewed in *(7)*, have investigated Greaves's prediction that infants with a high level of exposure to nonspecific infections would have a reduced risk of subsequent cALL, using, for example, birth order or day care attendance as proxies for exposure to infection. The results are mildly supportive overall, but they are not very consistent, and some may be complicated by bias or confounding. Other studies have looked for an increased risk of leukemia in children exposed to maternal influenza during gestation *(8–19)*, with inconclusive results. Exposure of the child to influenza shortly before the diagnosis of leukemia has not often been investigated. One case–control study *(8)* found that reported influenza infection of the child during infancy was associated with a statistically significant increase in risk of leukemia diagnosed at ages over 15 months and under 15 years, based on 116 cases diagnosed in New Zealand from 1990–1993. The authors comment that the finding could be a chance association due to multiple comparisons and small numbers of exposed children. A case–control study in Greece *(20)*, based on 94 cases of childhood ALL, identified exposure to 10 common infections directly, using serologic markers; there was no association with seropositivity for influenza A or influenza B. The time period covered by this study, 1993–1997, did not include either of the years of peak incidence in our data.

Our trend estimates are derived from a large, high-quality population-based registry. It is possible that there may have been some improvement in ascertainment during the study period, but if so, as outlined above, the proportion missed is estimated to have been very small, and it is unlikely that underascertainment could explain the differences in the trends for different types of leukemia. On the other hand, the coincidence of two small peaks in ALL with influenza epidemics may well be due to chance. Even if there is a real association, it may not be causal or it might be indirectly causal. There is no suggestion that influenza is the only infection that might trigger ALL, and, indeed, the role of influenza might be simply to reduce the level of immunity to other infections.

Our results suggest that cALL differs in etiology from other childhood leukemias and that some contributing factor for cALL has changed over time. They are consistent with hypotheses suggesting that some childhood leukemia may be triggered by infection occurring close to the time of diagnosis of leukemia, particularly in conditions of low herd immunity, and they raise the possibility that influenza may sometimes be involved.

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Notes

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