Aetiological clues from the descriptive epidemiology of childhood acute lymphatic leukaemia and other malignancies

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Studies in the US, Italy, UK and other countries have reported increases over time of the incidence rates of acute lymphatic leukaemia (ALL). We have previously reviewed the findings of studies published up to 2003: patterns have not been fully consistent across countries, and independent analyses of the US Surveillance Epidemiology and End Results programme (ie, the greatest available case series) have not provided unequivocal results.¹ A pooled analysis of European data carried out at the International Agency for Research on Cancer² estimated a statistically significant increase of 1.4% per year starting in 1970. This and other studies suggest an increase over time for all childhood cancers considered together and for most individual childhood cancer types, but with somewhat smaller increases than for ALL.

How should these observations be interpreted? Most studies are based on analyses of routine statistics such as those produced by population-based cancer registries. The data underlying the European findings² had been subjected to standardised procedures to evaluate quality of cancer registration, to uniform checks and to expert assessment. Whether or not these procedures ensure that registration has been uniformly exhaustive over the decades under observation is questionable. The processes for data collection are dynamic and it has been suggested that only recent data are adequate as a baseline for future monitoring.³ At least for ALL, relatively sophisticated and more sensitive techniques applied to data from our childhood cancer registry, such as the use of a generalised linear mixed model, provided a better insight into the year by year changes, but did not modify the estimates of the overall (positive) trend.¹

Should we trust that exhaustiveness of registration has not substantially improved in time, the observation of

increased cancer incidence would raise hypotheses about corresponding changes in environmental exposures or conditions of life. In fact, analytical epidemiological studies, mostly with a case-control design, given the rarity of childhood cancers, have not been successful in the identification of specific hazardous exogenous exposures.⁴

The fact that increases in incidence seem to occur for many different childhood malignancies at the same time requires some consideration. On the one hand, it detracts specificity to the phenomenon and gives some support to the idea that what is changing is the completeness of data collection. On the other hand, the question arises as to whether there is some overlap between the causes of different types of childhood cancer and

particularly between ALL and solid cancers. Two features typical of the distribution of ALL may provide some clues to aetiology: its tendency to cluster (although only a relatively small proportion of cases cluster) and the typical peak in occurrence around age 2–3 years, which is more pronounced in Western than in Eastern Europe and in recent times than in the past.² The evidence of a similar pattern of the age distribution of other childhood cancers is weak, although there is some suggestion of a tendency for clustering of brain⁵ and perhaps other childhood cancers.

In recent years, it has become obvious that population-based childhood cancer registries are essential to assess the quality of the delivery of care.⁶ We believe there is also a role for them in the determination of cancer aetiology, but research is needed to answer the following questions:

- In the production of current statistics on the incidence of childhood cancer, to what extent are there reliable criteria to retrospectively distinguish between actual increases in childhood cancer incidence and artefacts due to improved diagnostic and ascertainment criteria?
- How much extra information on temporal trends of childhood cancer can be obtained through analytical techniques alternative or complementary to the standard Poisson regression, such as generalised linear mixed models?

Key points

- There are suggestions that the incidence of childhood cancer is increasing, at least in European countries. However, our ability in distinguishing between real incidence increases and improved ascertainment criteria is inadequate, and confirmation that case registration has been exhaustive and constant in time is desirable.
- Intrauterine exposure to diagnostic x rays at doses which are nowadays obsolete is a proved risk factor for ALL. Compared with adult cancers, geographical differences in the incidence of childhood cancer are limited, which suggests a role of genetic factors although familial aggregation accounts for a minority of cases. Viral infections as explanation of some case of ALL has been recently reinforced by the observation of a relation between peaks in the incidence of ALL with years immediately after influenza epidemics.⁷ To date, for ALL as well as for other childhood cancers, there have been suggestions, but no definite confirmation, of a role of other putative aetiological factors such as very low frequency electromagnetic fields, parental occupational, and children's environmental exposures, socioeconomic factors, parental age, perinatal characteristics, and others. Tobacco smoke does not seem to be associated with childhood cancer.
- Even more than for adult cancer, for childhood cancer, the interaction between the above environmental and behavioural factors and between these and genetic characteristics is largely unknown.

- To what extent are differences/similarities of the distribution of individual childhood cancer types consistent with knowledge on risk factors?

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REFERENCES

- 1 **Maule MM**, Zuccolo L, Magnani C, *et al*. Bayesian methods for early detection of changes in childhood cancer incidence: trends for acute lymphoblastic leukaemia are consistent with an infectious aetiology. *Eur J Cancer* 2006;**42**: 78–83.
- 2 **Steliarova-Foucher E**, Stiller C, Kaatsch P, *et al*. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. *Lancet* 2004;**364**:2097–305.
- 3 **Adamson P**, Law G, Roman E. Assessment of trends in childhood cancer incidence. *Lancet* 2005;**365**:753.
- 4 **Stiller CA**. Epidemiology and genetics of childhood cancer. *Oncogene* 2004;**23**: 6429–44.
- 5 **McNally RJ**, Cairns DP, Eden OB, *et al*. An infectious aetiology for childhood brain tumours? Evidence from space-time clustering and seasonality analyses. *Br J Cancer* 2002;**86**:1070–7.
- 6 **Gatta G**, Capocaccia R, Stiller C, *et al*. Childhood cancer survival trends in Europe: a Eurocare Working Group Study. *J Clin Oncol* 2005;**23**:3742–51.
- 7 **Kroll ME**, Draper GJ, Stiller CA, *et al*. Childhood leukaemia incidence in Britain, 1974–2000: time trends and possible relation to influenza epidemics. *J Nat Cancer Inst* 2006;**98**:417–20.