available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

Childhood leukaemias and CNS tumours: Correlation of international incidence rates

Sarah J. Hepworth, Richard G. Feltbower, Patricia A. McKinney*

Paediatric Epidemiology Group, Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health and Therapeutics, 30-32 Hyde Terrace, University of Leeds, Leeds LS2 9LN, United Kingdom

ARTICLE INFO

Article history:
Received 25 May 2005
Received in revised form 5 July 2005
Accepted 14 July 2005
Available online 10 January 2006

Keywords:
Childhood cancer
International
Incidence rates

ABSTRACT

Childhood leukaemia has a potential infectious aetiology whilst infections may also be linked to paediatric central nervous system (CNS) tumours. Using data from 29 countries we investigated the correlation between international incidence rates of childhood leukaemia and CNS tumours, focusing on acute lymphoblastic leukaemia (ALL), astrocytoma and ependymoma-subtypes that are hypothesised to have an infectious aetiology. Relationships between incidence rates and national demographic factors were also examined using Pearson's correlation coefficient to quantify associations. Comparing two diagnostic categories of leukaemia with four groups of CNS tumours, a highly significant positive correlation was found between ALL and astrocytoma ($r = 0.57$, $P = 0.002$). Higher rates of ALL and CNS tumours were associated with increased affluence, with the strongest correlation for Gross Domestic Product per capita and CNS tumours ($r = 0.70$, $P < 0.001$). National incidence rates of childhood ALL and astrocytomas were highly correlated and this may reflect a common environmental cause whose origin may be infectious in nature. International incidence of ALL and CNS tumours were also correlated with economic related factors. Variation in levels of ascertainment may partially explain this, although childhood environmental exposures related to infections will also be affected by levels of affluence.

1. Introduction

The aetiology of childhood cancer is likely to be multi-factorial, given the heterogeneity in incidence, mortality and pathology between the diagnostic groups. The proportion of childhood cancers attributed to known genetic or inherited susceptibility is very small and therefore environmental exposures are likely to have an important part to play. For certain tumours in children, exposure to infections have been suggested as possible aetiological agents. Evidence is strongest for acute lymphoblastic leukaemia (ALL), the most common subtype (80%) of childhood leukaemia.[1–5] More recently it has been suggested that childhood central nervous system (CNS) tumours may also have links with infections,[6–8] with the strongest support being for the subtypes of astrocytoma and ependymoma.[6,9] However, the mechanism describing the role infections may play in the development of these conditions, whether it is through direct contact with a specific environmental contagion that may damage DNA or a rare autoimmune response to infection in general, is still unclear.

In the context of a common aetiology of specific tumours, we have investigated whether this was reflected in correlation between incidence rates. A previous international analysis suggested that ALL was highly correlated with diabetes, and that this observation might be explained by factors associated

* *Corresponding author:* Tel.: +44 113 343 4878; fax: +44 113 343 4877.
E-mail address: s.j.hepworth@leeds.ac.uk (S.J. Hepworth).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.07.036

with affluence.[10] We have extended this approach by comparing the incidence rates of leukaemia and CNS tumours to investigate whether the hypothesis of an infectious aetiology for ALL, ependymoma and astrocytoma was reflected in positive correlations between these subtypes. We also explored whether there was any correlation between the incidence rates of leukaemias, CNS tumours and their subtypes and demographic characteristics including indicators of affluence.

2. Patients and methods

World standardised international incidence rates of childhood cancer were extracted for the analysis.[11] Subtypes were classified according to the International Classification for Childhood Cancer (ICCC)[12] and correlations were calculated using Pearson's correlation coefficient. Due to small numbers all analyses were repeated using Spearman's rank correlation coefficient. As multiple tests were being carried out, *P*-values of 0.01 or less were chosen as being significant, this value was chosen to make the significance level more conservative than the usual cut off point of $P = 0.05$ without using a more formal method as there is much debate on the best correction to use.[13] It was also felt the Bonferronni correction would be too conservative due to the aetiological nature of the analysis. Only rates based on data from population based registers were used. If incidence rates from several registries within a country were available these were combined as an average rate weighted by the number of person-years covered by each register. Data from the registers themselves covered slightly different periods although the vast majority related to the 1980s and early 1990s.

2.1. *Data quality*

Data quality was assessed by the two markers used by Parkin and colleagues:[12] the percentage of cases without microscopic verification of diagnosis and the percentage of cases based on death certificate only. Data from 5 (10%) of the 52 countries listed, where over 40% of cases fell into these categories were excluded from analysis; 12 (23%) countries with registers flagged by Parkin and colleagues[12] as having possible inconsistencies were also excluded. A further 6 (12%) countries did not have incidence rates available for all the subtypes of interest. Of the 29 countries used in the analysis 18 had full, 7 partial and 4 had sparse national coverage by cancer registries and covered, on average 20573517 (range: 1936481–110839330) person-years.

2.2. *Variables of interest*

As well as considering correlations between the rates of leukaemia and CNS tumour subtypes, we investigated the association between these rates and national demographic factors. Economic related factors included were GDP per capita ($), infant mortality (per 1000 live births) and life expectancy (years).[14] To investigate possible links between childhood cancer and vitamin D,[15] latitude and average hours of sunshine per day for each country were also collected.

3. Results

A summary of the cancer incidence rates for the 29 countries are given in Table 1.

Correlations were calculated between total leukaemia and CNS tumour incidence and then between subtypes (Table 2). Correlation between CNS tumours and all leukaemias was positive but not statistically significant ($r = 0.25$, $P = 0.20$). A highly significant positive correlation was found between ALL and astrocytoma ($r = 0.57$, $P < 0.01$). A positive association was also found between incidence rates of ALL and ependymoma but this was not significant ($r = 0.19$, $P = 0.34$). Using Spearman's rank correlation gave similar results (data not presented).

Fig. 1 gives a scatterplot of world standardised ALL and astrocytoma incidence rates, illustrating the positive linear correlation. Recalculating the correlation coefficient excluding Vietnam and Sweden as two possible outliers reduced the correlation between the two subtypes ($r = 0.43$, $P = 0.03$).

When considering the correlations between the standardised cancer rates and several demographic factors (Table 3), the incidence of leukaemia was positively, though not significantly, associated with demographic factors linked with greater affluence, with rates increasing with greater GDP, lower infant mortality and longer life expectancy whereas for ALL a significant positive association with all three economic related factors was found. For CNS tumours, the correlation appeared stronger and was most highly associated with GDP per

Table 1 – Summary statistics for rates per 100,000 person-years

	Number	Mean	Standard deviation	Minimum	Median	Maximum
All cancers	29	13.09	1.79	7.37	13.21	15.87
All leukaemias	29	4.35	0.79	2.62	4.46	5.79
Acute lymphoblastic leukaemia	29	3.26	0.86	0.92	3.36	4.63
Acute non-lymphocytic leukaemia	29	0.67	0.14	0.39	0.66	0.94
All CNS tumours	29	2.52	0.80	0.68	2.70	4.10
Ependymoma[a]	28	0.27	0.10	0.04	0.29	0.43
Astrocytoma	29	1.05	0.43	0.04	1.03	2.22
Primitive neuroectodermal tumours	29	0.55	0.17	0.06	0.58	0.87
Other gliomas[a]	27	0.29	0.24	0.04	0.27	1.30

a 1 country did not have a rate for ependymoma and 2 countries did not have a rate for 'other gliomas'.

Table 2 – Pearson correlation matrix between world standardised international incidence rates of childhood leukaemias and CNS tumours by subtype for 29 countries

	All leukaemias	Acute lymphoblastic leukaemia	Acute non-lymphocytic leukaemia
All CNS tumours	0.246 ($P = 0.20$)	0.452 ($P = 0.01$)	0.138 ($P = 0.47$)
Ependymoma[a]	0.001 ($P = 1.00$)	0.189 ($P = 0.34$)	−0.019 ($P = 0.92$)
Astrocytoma	0.390 ($P = 0.05$)	0.574 ($P = 0.002$)*	0.177 ($P = 0.41$)
Primitive neuroectodermal tumours	0.205 ($P = 0.29$)	0.450 ($P = 0.014$)	0.185 ($P = 0.34$)
Other gliomas[a]	0.277 ($P = 0.16$)	0.295 ($P = 0.14$)	−0.247 ($P = 0.21$)

a 1 country did not have a rate for ependymoma and 2 countries did not have a rate for 'other gliomas'.
* $P \leqslant 0.01$.

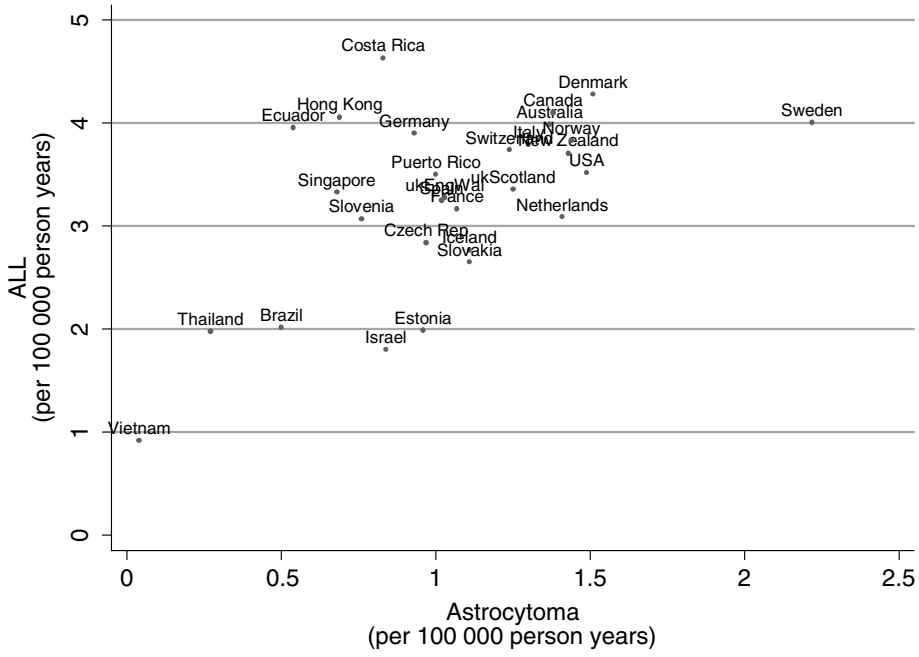

Fig. 1 – Scatter plot of world standardised international incidence rates for childhood acute lymphoblastic leukaemia (ALL) and astrocytoma ($n = 29$ countries).

Table 3 – Pearson correlation between world standardised international incidence rates of childhood leukaemias and CNS tumours (P-values given in brackets)

	Gross domestic product per capita ($) 1992	Infant mortality (per 1000 live births)[b] 1993	Life expectancy (years) 1993	Latitude (degrees from equator)	Sun (hrs per day)
All leukaemias	0.336 ($P = 0.08$)	0.283 ($P = 0.14$)	0.408 ($P = 0.03$)	−0.029 ($P = 0.88$)	−0.125 ($P = 0.52$)
Acute lymphoblastic leukaemia	0.504 ($P = 0.005$)*	0.454 ($P = 0.013$)	0.604 ($P = 0.001$)*	0.138 ($P = 0.47$)	−0.075 ($P = 0.70$)
Acute non-lymphocytic leukaemia	0.055 ($P = 0.78$)	−0.038 ($P = 0.84$)	0.036 ($P = 0.85$)	−0.141 ($P = 0.47$)	0.045 ($P = 0.82$)
All CNS tumours	0.697 ($P < 0.001$)*	0.633 ($P < 0.001$)*	0.664 ($P < 0.001$)*	0.764 ($P < 0.001$)*	−0.086 ($P = 0.66$)
Ependymoma[a]	0.512 ($P = 0.005$)*	0.564 ($P = 0.002$)*	0.577 ($P = 0.001$)*	0.603 ($P = 0.001$)*	−0.159 ($P = 0.42$)
Astrocytoma	0.697 ($P < 0.001$)*	0.636 ($P = 0.001$)*	0.680 ($P < 0.001$)*	0.678 ($P < 0.001$)*	−0.077 ($P = 0.70$)
Primitive neuroectodermal tumours	0.615 ($P < 0.001$)*	0.583 ($P = 0.001$)*	0.600 ($P = 0.001$)*	0.501 ($P = 0.006$)*	−0.073 ($P = 0.71$)
Other gliomas[a]	0.141 ($P = 0.49$)	0.292 ($P = 0.14$)	0.431 ($P = 0.03$)	−0.048 ($P = 0.81$)	0.109 ($P = 0.59$)

a 1 country did not have a rate for ependymoma and 2 countries did not have a rate for 'other gliomas'.
b Inverse used.
* $P \leqslant 0.01$.

capita ($r = 0.70$, $P < 0.01$), and also showing a positive association with lower infant mortality and longer life expectancy; similar results were found for all three major CNS tumour subtypes. Latitude was highly correlated with CNS tumour incidence, possibly due to it's correlation with economic related factors. No significant association was found between

hours of sunshine per day and any of the cancer incidence rates investigated.

4. Discussion

This first analysis of the correlation between international rates of leukaemias and CNS tumours indicated a highly significant positive association between international incidence rates of ALL and astrocytoma. The likelihood that this reflects a real effect is strengthened by the lack of such a strong correlation between the larger groupings of all leukaemias and all CNS tumours. The less significant correlations between ALL and all CNS tumours and astrocytomas and all leukaemias is likely to be accounted for by the ALL and astrocytoma relationship. No correlation was found between incidence rates of ependymoma and ALL. The remaining significant correlation between ALL and PNETs was not hypothesised prior to the analysis and may be explained by chance but merits further investigation.

A body of evidence now strongly points towards ALL having an infectious aetiology,[5] although further investigations are needed to clarify if this is also the case for CNS tumours, especially astrocytoma, and to consider the likelihood of both diseases having a common, underlying environmental cause; namely infectious exposures in childhood.

Performing analyses at the international-level may mask any subtle individual variation in incidence rates within countries. Ecological studies may also be subject to specific biases[16] but there is a place for these types of studies to generate findings that can be considered for further attention. Regional level investigation of correlations in incidence rates within countries may help to further characterise any relationship between incidence of leukaemia and CNS tumours in childhood.

For this analysis we tried to be representative by including incidence rates from countries throughout the world. No rates for countries in Africa ($n = 7$) were used in this analysis, the majority could not be included because information on rates for subtypes were not available, and so it is unknown if the conclusions reached can be applied to this population. Though the international incidence rates are from the nineties, they represent the most recent, comprehensive international dataset of childhood cancer that is available at present. More up to date figures for all childhood leukaemia and CNS subtypes for countries in Europe will soon become freely available through the Automated Childhood Cancer Information System (ACCIS) project.[17] We plan a more detailed analysis using these data.

Higher levels of ascertainment in developed countries due to greater availability of diagnostic tools and more complete cancer registration may explain the positive correlation found between some of the cancer incidence rates and economic related factors. This correlation was found for the international incidence rates of ALL and several economic related factors but not for the larger diagnostic grouping of leukaemia. The incidence rates of CNS tumours and its subtypes were all correlated with affluence. This suggests a possible real effect of affluence for ALL that may be due to more than just higher ascertainment, improved socioeconomic status will also have an influence on the type of environmental exposures experienced in childhood such as type and timings of contact with infections and vaccinations.

In the future, as more data becomes available from international organisations such as the World Health Organisation and the United Nations, more detailed analysis including adjustment for different environmental and economic related factors will be possible to determine which specific exposures show the strongest correlation with cancer incidence.

The aetiology of childhood cancers is highly complex involving a combination of genetic, biological and environmental factors.[18] Further investigation will be required to confirm the results found here and to identify the possible biological mechanism involved in the link between infectious exposure and the subsequent development of ALL and astrocytoma.

Conflict of interest statement

None declared.

Acknowledgements

Richard Feltbower is supported by funding from the Candlelighter's Trust. We thank Adam Wingfield for his assistance with collecting the demographic data.

REFERENCES

1. Little J. *Epidemiology of childhood cancer*, vol 149. Lyon,: IARC Science Publication, IARC; 1999.
2. Alexander FE, Boyle P, Carli PM, et al. on behalf of the EUROCLUS project. Spatial clustering of childhood leukaemia: summary results from the EUROCLUS project. *Br J Cancer* 1998;**77**:818–24.
3. Kinlen L. Epidemiological evidence for an infective basis in childhood leukaemia. *Br J Cancer* 1995;**71**:1–5.
4. Greaves M. Childhood leukaemia. *BMJ* 2002;**324**:283–7.
5. McNally RJQ, Eden TO. An infectious aetiology for childhood acute leukaemia: a review of the evidence. *Br J Haematol* 2004;**127**:243–63.
6. McNally RJQ, 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.
7. Fear NT, Roman E, Ansell P, et al. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors. *Cancer Cause Control* 2001;**12**:443–9.
8. Nyari TA, Dickinson HO, Hammal DM, et al. Childhood solid tumours in relation to population mixing around time of birth. *Br J Cancer* 2003;**88**:1370–4.
9. McNally RJQ, Alston RD, Eden TO, et al. Further clues concerning the aetiology of childhood central nervous system tumours. *Eur J Cancer* 2004;**40**:2766–72.
10. Feltbower RG, McKinney PA, Greaves MF, et al. International parallels in leukaemia and diabetes epidemiology. *Arch Dis Child* 2004;**89**:54–6.
11. Parkin DM, Kramárová E, Draper GJ, Masuyer E, Michaelis J, Neglia J, Qureshi S, Stiller CA, editors. *International incidence of childhood cancer*, vol. II. Lyon: IARC Science Publication No. 144., IARC; 1998.

12. Kramárová E, Stiller CA, Ferlay J, Parkin DM, Draper GJ, Michaelis J, Neglia J, Qureshi S, editors. *International classification of childhood cancer*. IARC Technical Report No. 29. Lyon: IARC; 1996.
13. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ* 1998;**316**:1236–8.
14. World Health Organisation. World health report: bridging the gaps. Geneva: World Health Organization; 1995. p. 101–12.
15. Ames BN, Wakimoto P. Are vitamin and mineral deficiencies a major cancer risk? *Nat Rev Cancer* 2002;**2**:694–704.
16. Greenland S, Robins J. Ecologic studies – biases, misconceptions and counterexamples. *Am J Epidemiol* 1994;**139**:747–60.
17. 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**:2097–105.
18. Stiller CA. Epidemiology and genetics of childhood cancer. *Oncogene* 2004;**23**:6429–44.