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Childhood leukaemias and CNS tumours: Correlation of international incidence rates

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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

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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'.