Childhood cancers: space-time distribution in Britain

E A Gilman and E G Knox

Abstract

Study objectives - To examine a national data set of all childhood cancers for evidence of space-time interactions within three distinct sets of dates and places (at birth, at diagnosis, and at death), to show whether the patterns found for these events represent separate phenomena or statistically interdependent processes, and to see whether the childhood leukaemias and the childhood solid cancers have separate distinctive patterns in these respects.

Design - This was a space-time cluster analysis. The large number of cases enabled division of the data into two sets, one for hypothesis generation and the other for hypothesis testing.

Setting - England, Scotland, and Wales.

Subjects - A national collection of 22 360 children aged 0–15 years with fatal cancers and leukaemias in the period 1953 to 1980.

Main results - There was significant clustering among the leukaemias and lymphomas on date and place of birth (particularly among cases born within 1 km and up to 5 months apart), and on date and place of diagnosis (particularly among cases diagnosed from 3 to 5 km apart and up to 9 months apart). There was no clustering among the solid cancers.

Conclusions - The birth clustering was significant among pairs diagnosed at differing ages, and diagnosis clustering was significant among pairs born at different times, and it was concluded that the two types of clustering must be regarded as separate and statistically independent phenomena. Both the birth and the diagnosis clusters comprised many independent pairs of cases, with no large multiple case clusters. This suggests the involvement of multiple time-space localised exposures to hazards with short and constant latent intervals; probably an infectious agent or an environmental toxin. Given the separate nature of the two types of clustering, exposure to more than one hazard may be involved.

It has been suggested that childhood leukaemias and cancers sometimes occur in small and transient clusters, and that this is consistent with either an infective cause or a focal-episodic toxic cause for the disease. Many workers have investigated clustering in relation to the date and place of onset, or of diagnosis, using a variety of methods.¹ The results have been inconsistent - some studies have found evidence of space-time clustering,²⁻⁶ while others have not.⁷⁻¹³ Some investigations have also examined childhood leukaemia data for clustering in relation to the date and place of birth. These studies have likewise provided some evidence, albeit weak evidence, of space-time clustering.¹⁰⁻¹³

Most published studies have consisted of relatively localised collections of cases (for example, for a county or city). Some have been based on anecdotal data, or on small data sets, and a range of space-time intervals have been examined for clustering. Sometimes, formal analyses have been based on intervals suggested by previous, less formal impressions of excesses within the same data set, and the statistical significance of the clustering is then difficult to assess. These difficulties are exacerbated by the large number of alternative time and distance comparisons available for testing, as well as the multiple opportunities for selecting an area for study because clustering was already suspected.

Only recently has a complete data set from a whole country become available for such examination.¹⁴ Even there, the data were limited to the dates and places of onset and a simultaneous analysis for clustering of dates and places of birth was not possible.

The study reported here gives the results of examining the space-time distributions of births, disease onset, and deaths within a national collection of children with fatal cancers and leukaemias in the period 1953 to 1980. With such a large number of cases (over 22 000), covering a broad geographical area, the data could be divided into two sets: one set to be used for hypothesis generation, including the definition of the distance and time criteria to be used subsequently; and the other set for hypothesis testing.

The objectives were: (i) to test for and to characterise any space-time interactions within 3 distinct sets of dates and places (at birth, at diagnosis, and at death) and to show whether patterns found for these different events represented separate phenomena or statistically interdependent processes; and (ii) to repeat the examination for the childhood leukaemias and solid cancers, both separately and together, to see whether these diagnostic groups show their own distinctive patterns.

Methods

The data are derived from the Oxford survey of childhood cancers (OSCC).¹⁴⁻¹⁶ The spatial
information consisted of the grid references (to
the nearest 100 m) of the home addresses at
birth and at death, for each of 22 360 children
(aged 0–15 years) in England, Scotland, and
Wales who had died of cancer or leukaemia
between 1953 and 1980 inclusive. The address
diagnosis was not separatedly recorded and
the address at death was used as a proxy for
the place of cancer diagnosis. The grid refer-
ences were obtained by matching the post-
codes of the case addresses with the Central
Postcode Directory, a computer tape of all the
postcodes in Britain (approximately 1.3 mil-
ion) together with their map coordinates.17
The temporal information available for each
case included the dates of birth, diagnosis, and
deat.

The data were divided into two sets, one
for hypothesis generation, and the other for
hypothesis testing. All cases who were born
or died in central Britain, between Ordnance
Survey grid lines 200-north and 400-north,
were analysed first (8750 cases in total). (Grid
line 200-north passes through Pembroke in
the west to just north of Warwick in the east.
Grid line 400-north passes through Liverpool in
the west to just south of Grimsby in the east.)
Data from the remaining cases were later used
to test specific hypotheses generated by the
"central" set.

Cases were excluded from space-time anal-
ysis if the date and place of the event of interest
were not known with sufficient accuracy. There
were 3261 cases born in the period 1953–64
within grid lines 200-north and 400-north, 2712
(83%) of these were used in the analysis of the
distribution of date and place of birth. Of the
cases excluded, 547 were because the full home
address at the time of birth was not obtained;
most (80%) of these exclusions were because
the case had not been interviewed by the
OSCC. Only two cases (both leukaemias and
lymphomas) were excluded from analysis be-
cause date of birth was not known. There was
very little difference between the proportion
of leukaemias and lymphomas excluded from
analysis (15%) and the proportion of solid
cancers excluded (18%).

For analysis of the date and place of cancer
diagnosis, address at death was used as a proxy
for address at diagnosis. There were 8128 cases
who died within central Britain, of these 592
(7%) were excluded from analysis, 590 because
the date of diagnosis was not known, and two
cases because both date of diagnosis and ad-
dress were not known. There was no difference
between the leukaemias and lymphomas and
the solid cancers in the proportion of cases
excluded from analysis.

For date and place of death, only 2 of the
8128 cases in central Britain were excluded from
analysis, both were patients with solid
cancers who had not been interviewed, whose
addresses at death could not be postcoded and
grid referenced with sufficient accuracy.

In the second data set, 7130 cases were born
outside central Britain in the period 1953–64,
and 4738 (67%) of these were used in the
analyses of the distribution of date and place
of birth, a lower proportion than was used in
the analyses of cases born in central Britain,
where 83% of cases were used. All of the cases
excluded were because the full home address
at time of birth was not obtained, most (82%)
of these exclusions were because the case had
not been interviewed by the OSCC. The rest
were interviewed cases for whom the address
at time of birth was not given in sufficient detail
to allow it to be accurately postcoded and
grid referenced. There was very little difference
between the proportion of leukaemias and
lymphomas excluded from analysis (32%) and
the proportion of solid cancers excluded (35%).

The other 14 625 cases who died outside
central Britain, of these 1567 (11%) were ex-
cluded from analysis of date and place of cancer
diagnosis, most because the date of diagnosis
was not known. There was practically no differ-
ence between the proportion of leuk-
amias and lymphomas (11%) and the pro-
portion of solid cancers (10%) excluded from
analysis.

For date and place of death, only 18 of the
14 625 cases outside central Britain were
excluded from analysis. All were cases whose
death addresses could not be postcoded and
grid referenced with the use of their map coor-
dinates. Data were postcoded for each of the
cases, but there were 147 cases who died in
Scotland and other parts of the British Isles
outside central Britain; all except 8 were ex-
cluded from analysis of date and place of death.

The distribution of cases in both space and
time was examined using the Knox method,
comparing the observed number of pairs of
cases within short time and space intervals
with the number expected if the temporal and
geographic distances between pairs were in-
dependent of each other. Significance was
tested by calculating a statistic, d, which is
distributed as the standard normal deviate.3,18
The confusing effects of a possible spatial-
temporal heterogeneity in the population at
risk, caused by shifts in population con-
centration over the long time period covered
by the data, were avoided by dividing the data
set into shorter time periods and using the
modified analysis described by Klauber and
Mustacchi.19 This produces a summary stat-
istic, d, which is also distributed as the standard
normal deviate. The application of the Knox
method to childhood cancer data, and the mo-
dification suggested by Klauber and Mustacchi
are described in more detail in Gilman and
Knox.7

Analyses were first performed for all cancers
together, and then separately for the leukaemias
and lymphomas grouped together, and for the
solid cancers. Some analyses were repeated
for two separate age groups: those under 60
months of age, and those aged 60 months or
older.

To avoid possible artefacts because of the
incompleteness of those birth cohorts for whom
a full 16 years of follow up were not available,
the analyses of date and place of birth were
carried out in the "completed" cohorts only—
that is, cases born between 1953 and 1964
inclusive. This was to avoid the possibility of
spatial/temporal heterogeneity in the extent to
which onsets and deaths might have been post-
poned beyond the time limits of case as-
certainment. Analyses of date and place of
diagnosis and of death were based on deaths
during the entire study period, 1953–80.
Results

The results of the Knox analyses are presented in Tables 1–10 (only tables 1, 2, 3, 5 and 7 are published here, the remainder are available from the authors). The range of space and time intervals used to test for clusters were: (space) <1 km, <2 km, <3 km, <4 km, <5 km, <10 km, <20 km; and (time) 0, <1, <2, <3, <4, <5, <6, <9, <12, <18, <24, <48 months. For clarity of presentation the tables show details for intervals up to 5 km and up to 12 months only. The numbers within particular intervals are cumulative; for example, pairs of cases born within 3 km and 3 months of each other include those pairs born within 2 km and 3 months, and they in turn include pairs born within 2 km and 2 months, and so on.

Table 1

<table>
<thead>
<tr>
<th>Time (&lt;km)</th>
<th>Pairs</th>
<th>O/E</th>
<th>(Cases)</th>
<th>All distances</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7</td>
<td>1-41</td>
<td>(14)</td>
<td>158</td>
</tr>
<tr>
<td>1</td>
<td>1-23</td>
<td>(36)</td>
<td>(100)</td>
<td>1435</td>
</tr>
<tr>
<td>2</td>
<td>1-32</td>
<td>(64)</td>
<td>(252)</td>
<td>1435</td>
</tr>
<tr>
<td>3</td>
<td>1-27</td>
<td>(85)</td>
<td>(340)</td>
<td>1435</td>
</tr>
<tr>
<td>5</td>
<td>1-51</td>
<td>(101)</td>
<td>(382)</td>
<td>1435</td>
</tr>
<tr>
<td>10</td>
<td>1-59</td>
<td>(114)</td>
<td>(426)</td>
<td>1435</td>
</tr>
<tr>
<td>12</td>
<td>1-30</td>
<td>(212)</td>
<td>(660)</td>
<td>1435</td>
</tr>
<tr>
<td>All</td>
<td>710</td>
<td>(877)</td>
<td>(1488)</td>
<td>1435</td>
</tr>
</tbody>
</table>

O/E = ratio of observed number of pairs to expected number.

*Crude O/E significantly different from 1-00, p<0.05.
† O/E remained significant after calculation of d, (see text). Time and space intervals are cumulative.

Table 2

<table>
<thead>
<tr>
<th>Time (&lt;km)</th>
<th>Pairs</th>
<th>O/E</th>
<th>(Cases)</th>
<th>All distances</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>1-86</td>
<td>(16)</td>
<td>1435</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>1-00</td>
<td>(171)</td>
<td>1435</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>1-11</td>
<td>(212)</td>
<td>1435</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>1-00</td>
<td>(114)</td>
<td>1435</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>1-12</td>
<td>(155)</td>
<td>1435</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>1-07</td>
<td>(188)</td>
<td>1435</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>1-06</td>
<td>(331)</td>
<td>1435</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>1-03</td>
<td>(408)</td>
<td>1435</td>
</tr>
<tr>
<td>8</td>
<td>84</td>
<td>1-09</td>
<td>(578)</td>
<td>1435</td>
</tr>
<tr>
<td>9</td>
<td>94</td>
<td>1-04</td>
<td>(709)</td>
<td>1435</td>
</tr>
<tr>
<td>12</td>
<td>95</td>
<td>1-01</td>
<td>(914)</td>
<td>1435</td>
</tr>
<tr>
<td>All</td>
<td>602</td>
<td>(607)</td>
<td>(1012)</td>
<td>1435</td>
</tr>
</tbody>
</table>

O/E = ratio of observed number of pairs to expected number. Time and space intervals are cumulative.

DATE AND PLACE OF BIRTH

The children with leukaemias and lymphomas born in central Britain clustered on date and place of birth (table 1). They showed excesses of pairs born within a range of short time intervals (up to 5 months) and short distances (up to 5 km) of each other. For example, there were 84 pairs born within 5 km and in the same month, against an expected value of 66-14. The birth clusters included pairs with onsets at widely varying ages. Clustering was present among pairs who were both diagnosed below 60 months of age, and in pairs who were both diagnosed aged 60 months or older; and there was also significant space-time clustering among age cross-pairs, pairs where each onset was in a different age group.

By contrast (table 2), the solid cancers showed no significant space-time interactions on date and place of birth, and had few observed: expected (O/E) ratios large enough to suggest clustering; the largest being for pairs born within 1 km or 2 km and in the same month. Among all cancers combined, the pattern of clustering resembled that of the leukaemias and lymphomas, but with smaller O/E ratios, probably reflecting the dilution of the leukaemia/lymphoma clustering by the non-clustering of the solid cancers.

These initial findings suggest that space-time birth clustering is concentrated in the leukaemias and lymphomas; and the data from the rest of Britain confirmed this. The patterns of birth clustering were repeated for the leukaemias and lymphomas, particularly those born within 1 km and up to 5 months apart (table 3), but were absent for the solid cancers (table 4: available from the authors).

In neither the central nor the wider data set were there significant interactions among the diagnosis cross-pairs (where each member of the pair was from a different diagnostic group), reinforcing the conclusion that the space-time distribution of the leukaemia/lymphoma births is different from that of the solid cancer births.

The consistency of the findings in both parts of the country weakens the possibility that the leukaemia and lymphoma birth clusters could be the result of a statistical or a regionally limited ascertainment artefact.

DATE AND PLACE OF DIAGNOSIS

In addition to the birth clustering, there was evidence of clustering on date and place of diagnosis in the data for central Britain (table 5). Again, this was present among the leukaemias and lymphomas, but not among the...
Table 3 Knox space-time analyses of date and place of birth: leukaemias and lymphomas outside central Britain 1953–64 (2478 cases)

<table>
<thead>
<tr>
<th>Time (&lt;mth)</th>
<th>Space (&lt;km)</th>
<th>All distances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>Pairs</td>
<td>O/E</td>
</tr>
<tr>
<td>0</td>
<td>15</td>
<td>1.75</td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>1.28</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>1.29*</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
<td>1.24*</td>
</tr>
<tr>
<td>5</td>
<td>118</td>
<td>1.27†</td>
</tr>
<tr>
<td>6</td>
<td>132</td>
<td>1.21*</td>
</tr>
<tr>
<td>9</td>
<td>171</td>
<td>1.08</td>
</tr>
<tr>
<td>12</td>
<td>217</td>
<td>1.06</td>
</tr>
<tr>
<td>All Times</td>
<td>1230</td>
<td>1.24</td>
</tr>
</tbody>
</table>

O/E = ratio of observed number of pairs to expected number.

*Crude O/E significantly different from 1.00, p<0.05.† O/E remained significant after calculation of d, (see text). Time and space intervals are cumulative.

Table 5 Knox space-time analyses of date and place of diagnosis: leukaemias and lymphomas in central Britain 1953–80 (3862 cases)

<table>
<thead>
<tr>
<th>Time (&lt;mth)</th>
<th>Space (&lt;km)</th>
<th>All distances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>Pairs</td>
<td>O/E</td>
</tr>
<tr>
<td>0</td>
<td>15</td>
<td>1.16</td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>1.12</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>1.19</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td>132</td>
<td>1.15</td>
</tr>
<tr>
<td>5</td>
<td>154</td>
<td>1.15*</td>
</tr>
<tr>
<td>6</td>
<td>186</td>
<td>1.00</td>
</tr>
<tr>
<td>9</td>
<td>262</td>
<td>1.11*</td>
</tr>
<tr>
<td>12</td>
<td>339</td>
<td>1.10</td>
</tr>
<tr>
<td>All Times</td>
<td>3944</td>
<td>1.10</td>
</tr>
</tbody>
</table>

O/E = ratio of observed number of pairs to expected number.

*Crude O/E significantly different from 1.00, p<0.05.† O/E remained significant after calculation of d, (see text). Time and space intervals are cumulative.

Discussion

POSSIBLE CAUSES OF ARTEFACTUAL SPACE-TIME CLUSTERING

Firstly, consideration must be given to the possibility of artefactual causes for the space-time clustering within these data. Cases had been excluded from the reported analyses if the date and place of the event of interest were not sufficiently precise. This was done in the interests of accuracy, but might have resulted in clustered exclusions. However, the exclusion rates were similar among the leukaemias/lymphomas and solid cancers, although the patterns of clustering in these diagnostic groups were different. The greatest proportion of exclusions related to the address at birth, so
Table 7 Knox space-time analyses of date and place of diagnosis: leukaemias and lymphomas outside central Britain 1953–80 (6511 cases)

<table>
<thead>
<tr>
<th>Time (§month)</th>
<th>Space (&lt;km)</th>
<th>All distances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>Pairs</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>1-20</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(58)</td>
</tr>
<tr>
<td>1</td>
<td>Pairs</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>1-21</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(172)</td>
</tr>
<tr>
<td>2</td>
<td>Pairs</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>1-13</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(263)</td>
</tr>
<tr>
<td>3</td>
<td>Pairs</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>1-10</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(354)</td>
</tr>
<tr>
<td>4</td>
<td>Pairs</td>
<td>236</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>1-08</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(451)</td>
</tr>
<tr>
<td>5</td>
<td>Pairs</td>
<td>299</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>1-12†</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(561)</td>
</tr>
<tr>
<td>6</td>
<td>Pairs</td>
<td>355</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>1-13*</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(649)</td>
</tr>
<tr>
<td>9</td>
<td>Pairs</td>
<td>488</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>1-06</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(864)</td>
</tr>
<tr>
<td>12</td>
<td>Pairs</td>
<td>633</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>1-05</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(1075)</td>
</tr>
<tr>
<td>All Pairs</td>
<td>Times</td>
<td>7303</td>
</tr>
<tr>
<td></td>
<td>(Cases)</td>
<td>(4792)</td>
</tr>
<tr>
<td></td>
<td>O/E</td>
<td>ratio of observed number of pairs to expected number.</td>
</tr>
<tr>
<td></td>
<td>* Crude O/E significantly different from 1-00, p&lt;0-05.</td>
<td></td>
</tr>
</tbody>
</table>
|               | † O/E remained significant after calculation of d, (see text). Time and space intervals are cumulative.

The impact of the birth-place exclusions was assessed by repeating the analyses using place of death as proxy if the place of birth was not available. The results were similar, although at reduced levels of significance.

The diagnosis clusters could have been the result of clustered failures to recognise the diagnosis, or to clustered recognition and reporting of cases, where the discovery of an initial case had led to increased local vigilance. However, this second contingency would have led to corresponding deficits of pairs of cases separated by somewhat longer time intervals; and no such deficits were found. In addition, clustering on date and place of diagnosis was recently reported in a data-set exhibiting very high levels of ascertainment. This consisted of childhood leukaemias and non-Hodgkin's lymphomas registered in Britain between 1966 and 1983. Space-time clustering was again present among pairs of all ages, within separate age bands, and among age band, cross-pairs. Ascertainment among this set of cases (which included both fatal and non-fatal cases) was around 99%, and effectively excludes the proposition that localised variations in the reporting and diagnosis of cases could explain the clusters.

This conclusion is strongly supported by the consistent difference in clustering behaviour between the leukaemias and the lymphomas on the one hand, and the solid cancers on the other; and by the consistency of both findings in different parts of the country.

Artefactual birth clustering can result from the presence of concordant twins; and a genetically determined similarity of their latent periods could lead to clustering of their dates and places of diagnosis. The data set used for the analyses of birth clustering (cases who were born between 1953 and 1964 inclusive) included one pair of twins concordant for malignant oligodendroglioma (born in central Britain). For the analyses of diagnosis clustering the data included this pair (diagnosed in central Britain) and two pairs concordant for leukaemia (diagnosed outside central Britain). The oligodendroglioma diagnoses were separated by 48 months. One leukaemia pair was diagnosed in the same month, and the other pair separated by 22 months. The removal of these twin pairs from the data did not change the pattern or significance of the clustering already described.

EPIEMIOLOGICAL INTERPRETATION OF FINDINGS

One of our objectives was to see whether different diagnostic groups of childhood cancer exhibited different and characteristic clustering patterns. The analyses showed that the leukaemias and lymphomas cluster on date and place of birth, and on date and place of diagnosis, but that the solid cancers do not. These findings were confirmed in two separate analyses of two separate sets of data.

Another objective was to see whether the clustering patterns of different events at different ages were statistically inter-related, or whether they represented separate phenomena – the diagnosis clustering “primary” and solely related to events around the time of diagnosis; or is it “secondary” to birth clustering, reflecting the delayed effects of prenatal or perinatal events? This question has been raised before, but without simultaneous information on both births and onsets, the authors were unable to resolve it fully.

Clustering of dates and places of diagnosis could be secondary to birth clustering only if there was little or no migration between the times of birth and diagnosis, and if the latent period between cancer initiation and promotion were nearly constant. Secondary diagnosis clusters would then be concentrated among pairs diagnosed at similar ages. However, primary diagnosis clustering, depending upon contemporary events rather than upon clustered birth events, would not necessarily be age concordant.

All the evidence presented here denies the possibility that the later (diagnosis) clustering is secondary to the earlier (birth) clustering. Firstly, as was discussed earlier, the birth clustering found in the leukaemias and lymphomas was significant among pairs with different ages at diagnosis, indicating that the period between cancer initiation and recognition is variable. Secondly, diagnosis clustering itself does not seem to be age group specific: it was present in the cross-pairs between age groups (and hence between birth cohorts), and the space-time interactions among the age cross-pairs were similar to the pattern shown by the analysis of pairs of all ages. It should be noted that the age heterogeneity of the diagnosis clusters
Childhood cancers clusters

is also incompatible with the hypothesis that the birth clusters could be statistically secondary to the diagnosis clusters.

The results of the analyses reported here therefore support the assertion that, among the leukaemias and lymphomas, clustering on date and place of diagnosis and clustering on date and place of birth are both “primary”. The birth clustering was significant among pairs diagnosed at differing ages, and diagnosis clustering was significant among pairs born at different times. The two types of clustering must be regarded as separate and statistically independent phenomena.

POSSIBLE BIOLOGICAL MECHANISMS

The leukaemia and lymphoma clusters comprised many independent pairs of cases, with little sharing of cases between different pairs, and there were no large multiple case clusters. This suggests the involvement of multiple time-space localised exposures to hazards with short and constant latent intervals; probably an infectious agent or an environmental toxin. Given the separate nature of the two types of clustering, exposure to more than one hazard may be involved.

Such exposures, either during the pregnancy or around the time of birth, could induce space-time patterns of the kinds observed for date and place of birth. If a toxic source were involved, the widespread geographical scatter of the leukaemia and lymphoma clusters would necessitate its common presence in residential areas, but fluctuating in the severity of emission or the closeness of contact. If an infectious agent were involved, it must also be quite widespread. Upper respiratory diseases during pregnancy have been associated with an increased risk of leukaemia or lymphoma for the unborn child. and these, together with the treatments they involve, must stand as candidates.

The diagnosis clusters could represent “promotion” events which either accelerate the disease process, or prompt haematological examinations which lead to the recognition of the leukaemia. Local epidemics of infections might interact with pre-leukaemic children, whose immune systems are already under stress, to produce clustered onsets of symptoms. However, there is recent evidence that acute space-time clustering may be superimposed on a longer term tendency towards geographical clustering, which would be more difficult to explain in these terms. A common process may be involved in both the space-time and the geographical concentrations, perhaps a repeated exposure to some locally fluctuating oncocgenic agent. Concentrations of children may have been “initialized” by earlier micro-epidemics of infection, possibly before birth, and the onsets triggered by reinfection, or by a toxic suppression of immunity.

We would like to acknowledge the help received from Dr A M Stewart and Mr G W Kneale in using the data held by the Oxford Survey of Childhood Cancers. This study was carried out as part of a research programme funded by the Medical Research Council (project grant number G8603397) and subsequently by the Three Mile Island Public Health Fund (USA).