

Space-time interactions in childhood cancers

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Abstract

Study objective—The aim of the study was to examine a cohort of cases of childhood cancer occurring in a defined geographical area to try to identify clustering and possible causative factors.

Design—Data were analysed using the close pair method developed by Knox for signs of clustering in relation to date and place of onset or date and place of birth.

Setting—Cases were those occurring in the 8 year period between 1953 and 1960 in four old counties of the Midlands of England (Worcestershire, Warwickshire, Staffordshire, Shropshire).

Cases—418 children under 10 years developed cancers during the study period: leukaemia 228, cerebral tumour 99, neuroblastoma 45, nephroblastoma 46. It is thought that data collection was complete. Cases were matched for region, sex and date of birth with live controls.

Results—There was evidence among some age groups and diagnoses of an unexpectedly high number of close pairs of onsets, and some indication of similar patterns among births of children who later developed cancer. The pre- and postnatal experiences of children involved in close pairs were examined to see whether they differed from those of control children. Measles appeared to occur more often in the 2-3 years before the onset of leukaemia in children who were later involved in close pairs than in their matched controls.

Conclusions—Common infectious diseases of childhood may play a minor role in the development of some cancers. Epidemics of these diseases may then be reflected on a greatly reduced scale in the subsequent distribution of cancer cases.

During the last twenty five years, there have been sporadic published reports of cases of childhood leukaemia occurring in clusters. The mathematical bases of these reports have sometimes been inadequate but the difficulty of detecting clustering in a disease which is so rare that it can never produce a genuine epidemic should not be underestimated. The fact that the debate has continued for so long suggests that clustering, if it occurs at all, must be a weak effect which is difficult to detect against the background "noise". Renewed interest in the topic, following suggestions that clusters may occur in the vicinity of nuclear establishments,¹⁻⁴ has prompted this report of an investigation into 418 childhood cancer cases which occurred in the Midlands

between 1953 and 1960. The data have not previously been published but the study produced some results which may be pertinent to today's debate on the vexed question of clustering and, if it can be shown unequivocally to exist, on its causative agents.

Methods

COLLECTION OF DATA

Short of an epidemic, clustering can only be confirmed or refuted by repeated application of appropriate tests to large numbers of cancer cases which have not been chosen simply because they looked promising in this respect—a criterion not always satisfied by other investigations. The present study relates to 418 children who developed various types of cancer before the age of 10 during the eight year period from 1953 to 1960. The children all lived in four old counties in the Midlands, namely Worcestershire, Warwickshire, Staffordshire and Shropshire, which together formed an area of approximately 11 000 km² in which there were no known nuclear installations. Just over half of the children (228) had leukaemia and the remainder suffered from cerebral tumour (99 cases), neuroblastoma (45 cases) and nephroblastoma (46 cases). Data were available from two sources so that almost every case in the region was probably included. The Oxford Survey of Childhood Cancers had records of all cancer deaths before the age of 10 years in England, Scotland and Wales and the Regional Cancer Registry in Birmingham claimed to know of all live and dead cases in the area.

In general, more information was available for the 380 fatal cases than for the 38 live cases because the Oxford Survey had additional data on 80% of the fatal cases obtained direct from the children's mothers and from hospitals and clinics concerned with the illnesses and with the relevant pregnancies. For these cases there were also comparable data for live controls, each of whom was matched for region, sex and date of birth with one of the fatal cases. Each of the 418 cases was characterised by two coordinates—a time coordinate which specified the month in which the child became unwell and a space coordinate which identified the geographical position of the child's home address. A few records were incomplete so that in six of the cases there was no record of onset date, only date of death. For each of these, an estimated onset date was obtained on the assumption that the duration of the illness corresponded with the modal duration experienced by those children in England and Wales in the Oxford Survey who had died (1) of the same disease; (2) in a three year period centred on the year in which the child died; (3) in a three

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Accepted for publication
July 1989

year age group centred on the child's age at death. Home addresses at the time of onset were available for the 38 live cases but the fatal cases had all to be positioned according to their home address at the time of death. The space coordinate consisted of the six figure National Grid reference (measured to the nearest 0.1 km in the easterly and northerly components) of the home address.

METHOD OF ANALYSIS

At the time when this study took place several methods were in use to test for clustering. These ranged from the purely intuitive, in which an unusually high number of cases was felt to exist, to the more rigorous, such as those developed by Knox⁵ or David and Barton.⁶ No method appeared to be entirely suitable but the approach was generally to divide the cases into groups based on a consideration of one of the two coordinates (eg, time groups were used by Barton *et al*⁷) and then to measure the within group variation of the second (eg, spatial) coordinate.

The present study used the close pair method devised by Knox. It has the advantage not only of being the simplest, but also of being insensitive to clustering in time alone, or in space alone, and of requiring no special knowledge of the population from which the cases were drawn. Using the time and space coordinates already identified, each of n cases in the series is paired with every other case to produce $n(n-1)/2$ pairs. The pairs are examined for signs of space-time interactions, defined as two or more cases located within a critical distance of each other and occurring within a critical time period. Pairs are classified according to whether they are "close" or otherwise and the expected number of pairs close in both dimensions (assuming no interaction) is calculated from the proportions of all pairs which are close in each dimension separately. The disadvantages are that there are no hard and fast rules about what constitutes a critical distance or a critical time and it may be difficult to decide whether or not a significant departure from expectation has occurred. The second difficulty stems from the fact that pairs of cases are not independent of one another since if two cases are close to a third they are bound to be fairly close to one another. Knox considered that the distribution of the number of close pairs on the null hypothesis approximated to a Poisson distribution so long as the critical distances and intervals were small enough to ensure a high probability of their being independent of one another. In the present study, a Poisson distribution was assumed when the expected number of close pairs was below 20. This assumption appeared to be justified since the ratio of the mean to the variance of the test statistic was fairly close to unity, as would be expected for a true Poisson distribution. The complete series of 418 cases and various subsets of cases, defined on the basis of type of cancer or of age at onset, were analysed over a range of critical times and distances according to the close pair method. In addition, since it is possible that key events in cancer causation may occur before or shortly after birth, a second analysis was performed in order to look for close pairs of births. It was a simple task to replace date of onset with date of birth but the place of birth was more difficult to ascertain. On

the assumption that, at that time, few children moved house before they were six, the second analysis was confined to children below this age at onset and the same spatial coordinate was used in the birth analysis as in the onset analysis. It was possible to test the validity of this assumption by considering the experience of 191 live controls matched with the fatal cases in the Oxford Survey. Less than 14% of these children had moved house in the period between birth and the age at which onset occurred in the child to whom they were matched.

Results

GROUP 1. LEUKAEMIA ONSETS, 228 CASES UNDER 10 YEARS OF AGE

This group contained all leukaemic children in the study. The results are given in table I and

Table I Analysis of 228 leukaemia onsets (all cell types) occurring before the age of 10 years.

Number of pairs	
Examined in total	25 875
Within 0.5 km	17
Within 15 months	7850
Within 0.5 km and 15 months	
observed	10
expected	5.16
Poisson p	0.038
mean/variance	1.44

show that at critical dimensions of 0.5 km and 15 months there were 10 close pairs compared with 5.16 expected on the null hypothesis ($p < 0.04$, Poisson distribution). The interaction was not confined to any particular cell type and no child was involved in more than one close pair. The mean/variance ratio was 1.44.

GROUP 2. CANCER ONSETS, 102 CASES OVER 6 YEARS OF AGE

Space-time interactions were more evident among the 102 cases over 6 years of age than in any other group. Numbers of close pairs exceeded expectation at critical dimensions above 1 km and 2 months. The effect appeared to be strongest at 3 km where there were 22 close pairs at 8 months

Table II Analysis of 102 cancer onsets (leukaemia and other cancers) occurring in the age range 6-9 years.

Number of pairs		
Examined in total	5151	
Within 3 km	70	
Within 8 months	855	
Within 12 months	1255 (cumulative figures)	
Space-time pairs:	3 km and 8 months	3 km and 12 months
observed	22	28
expected	11.62	17.05
Poisson p	0.004	0.009
mean/variance	1.22	1.34

compared with 11.62 expected (Poisson $p < 0.004$). Of the 37 children in the 22 pairs, 20 had leukaemia, 13 had cerebral tumours, three had neuroblastomas and one had neuroblastoma. The mean/variance ratio was 1.22. The results are summarised in table II.

GROUP 3. BIRTHS OF 304 CHILDREN WHO LATER DEVELOPED LEUKAEMIA (162 CASES) OR OTHER CANCERS (142 CASES)

Inaccuracies arising from the assumption of the equivalence of geographical location at onset with place of birth should be borne in mind when interpreting table III. This shows that an

Table III Analysis of births of 304 children who later developed leukaemia or other cancers

	Number of pairs		
	Leukaemia, 162 births	Other cancers, 142 births	Combined, 304 births
Examined in total	13 041	10 011	46 056
Critical dimensions:	2 km, 248 d	3 km, 155 d	2 km, 93 d
Within critical distance	116	168	404
Within critical time	1689	792	2212
Close in space and time, observed	24	21	28
expected	15.02	13.29	19.40
Poisson p	0.020	0.030	0.039
Mean/variance	1.13	1.09	1.04

unexpectedly high number (Poisson $p < 0.04$) of close pairs of births were obtained for (1) 162 children who later developed leukaemia with critical distances between births of 2 km and 248 d (24 close pairs compared with 15.02 expected), (2) 142 cancers, 3 km and 155 d (21 close pairs against 13.29 expected), (3) 304 leukaemias and other cancers combined, 2 km and 93 d (28 pairs against 19.40 expected).

DETAILED STUDY OF CLOSE PAIRS

In the second phase of the study, children who were members of the special pairs, ie, the ones who were unexpectedly close together according to the criteria outlined above, were identified and their pre- and postnatal experiences examined to see whether they differed significantly from those of other children in the same group. The relevant data were available only for children in the Oxford Survey (ie, survivors were not included) and for their matched controls. Particular attention was given to infections experienced by children involved in close onset pairing and to prenatal events in those linked to birth pairing. Although none of the four prenatal events studied (toxaemia, anaemia, chest x ray and abdominal x ray) appeared to have any significance in relation to unusual pairings of births, the timing of the common infectious diseases of childhood showed some interesting features in relation to onset pairing. Two different analyses were carried out.

Test based on binominal approximation

Illness records were screened for cases and for their matched controls. The occurrence of measles, for example, at any time before onset (or corresponding date for the control) was denoted by the number 1, and its absence by 0. The data were arranged in sets of two; the first figure of a set referred to a case and the second to its matched control (eg, 0,1 signified that the control, but not the case, had had measles). All case/control sets which produced 0,0 or 1,1 were then ignored. If there were a (0,1) sets of figures and b (1,0) sets among a particular group, then, on the null hypothesis, true values of a and b are equal. Thus, from tables of a binominal distribution with parameters 0.5 and $a+b$, the probability of obtaining a value more extreme than the observed value of a could be found. A two tail test was used and the analysis was applied to children in close pairs, other children in the same group, and to totals formed by both sets of children. It was repeated separately on data relating to pertussis and chicken pox and to all six infectious diseases of childhood (measles, pertussis, chicken pox, rubella, mumps and scarlet fever) taken together.

In addition, it was carried out for each of the periods 0-1, 2-3, and 4 or more years before onset.

When the test was applied to the children identified in groups 1 and 2 above, two results approached the 5% level of significance. In group 1, data relating to infectious diseases were available for 18 of the 20 children involved in 10 close pairs and for their matched controls. During the 2-3 years before onset of leukaemia, measles appeared to occur more frequently in children later involved in close pairs than in their matched controls. There were no (0,1) case/control sets of data but five (1,0) sets ($p = 0.06$, binomial two tail test). This trend was not repeated when similar data, which were available for 176 of the 208 case/control pairs in the remainder of the group, were analysed in the same way (table IV). In contrast, the opposite pattern emerged in an analysis of older children (group 2 above, all diagnoses, onsets 6-9 years of age, records available for 33 of 43 children involved in 28 close pairs at 3 km and 12 months, and for 46 of 59 children not closely paired). Taking all infections together (ie, 0,1 signified that the control but not the case had experienced at least one of the six common infections) in the entire period from birth to onset there were five (0,1) sets and no (1,0) sets amongst close pairs ($p = 0.06$, binomial two tail test) but no unusual patterns amongst other children in the same group (table V). In other words, there was some suggestion of a relative absence of one or more of the infectious diseases of childhood amongst older children who were later involved in close pairs of cancer onsets.

Test based on normal approximation

The previous test took no account of the numbers of infections recorded by cases and their matched controls. A second test, based on a normal approximation, was designed to compare the experience in this respect of children involved in special pairs with that of other children. The number of infectious diseases experienced by a case and by its matched control before the date of onset was recorded. A value was then computed for d (case score minus control score). If there were n case/control sets in a particular group of children, then on the null hypothesis d has a mean of zero, ie, cases and their matched controls experience, on average, the same number of infectious diseases. Thus, since d will be approximately normally distributed if n is reasonably large, the value of $\bar{d}/SE(\bar{d})$ could be tested against tables. A two tail test was used and the children were divided into subgroups on the basis of close pairings as in the previous test. There were no results of significance in group 1 but in group 2 there appeared to be a significant absence of infections amongst children involved in the special pairs (table VI, $p = 0.01$ for 33 children in close pairs). There was no comparable effect among the records of 46 children who were not members of special pairs and no results of significance when the intervals 0-1, 2-3 and 4 or more years before onset were analysed separately.

Discussion

Results of the first part of the present study were roughly in line with those of other investigations carried out at about the same time, ie, there

Table IV Group 1, case/control incidence of measles

	Interval in years measles to onset											
	0-1			2-3			4+			0-9		
	a	b	p	a	b	p	a	b	p	a	b	p
Close pairs (18 ca/ct sets)	1	0	-	0	5	0.06	2	0	-	2	4	-
Other children (176 ca/ct sets)	30	20	0.20	17	24	-	10	14	-	30	29	-
Total (194 ca/ct sets)	31	20	0.16	17	29	0.10	12	14	-	32	33	-

a = number of (0,1) sets of figures; b = number of (1,0) sets of figures; p = probability level, shown for $p \leq 0.20$, binomial approximation, two tail test

Table V Group 2, Case/control incidence of at least one of six infectious diseases

	Interval in years infection to onset											
	0-1			2-3			4+			0-9		
	a	b	p	a	b	p	a	b	p	a	b	p
Close pairs (33 ca/ct sets)	8	3	-	9	5	-	10	5	-	5	0	0.06
Other children (46 ca/ct sets)	6	9	-	11	14	-	9	9	-	3	4	-
Total (79 ca/ct sets)	14	12	-	20	19	-	19	14	-	8	4	-

a = number of (0,1) sets of figures; b = number of (1,0) sets of figures; p = probability level, shown for $p \leq 0.20$, binomial approximation, two tail test

Table VI Group 2, Incidence of common infectious diseases

	Close pairs (33 ca/ct records)	Other children (46 ca/ct records)	Total (79 ca/ct records)
\bar{n}	33	46	79
\bar{d}	-0.67 p=0.01	+0.33 p=0.20	-0.09
SE \bar{d}	0.26	0.25	0.19
$\bar{d}/SE\bar{d}$	2.6	1.3	0.5

\bar{d} = mean (case score minus control score)

p = probability level, shown for $p \leq 0.20$, normal approximation, two tail test

seemed to be some suggestion that weak onset clustering is a feature of some childhood leukaemias. Some investigators had suggested that the effect was confined to young children but a certain amount of variation between studies as to critical dimensions, age groups and types of leukaemias involved would be expected if the effect was weak and was superimposed on considerable background noise. In addition, the present data seemed to indicate that onset clusters may exist among older children and that these may be more apparent if all types of cancer are treated as a single disease. This would be reasonable if some common factor was involved in the genesis of these cancers. Data used in the birth analysis were less reliable than in the onset analysis, but there seemed to be some suggestion in the present study that clusters of births may exist among children who develop cancer at a relatively early age. This could indicate that some prenatal event was of significance.

Knox's close pair analysis is not capable of distinguishing between pairs of cases in which one member of the pair is a direct consequence of the other (eg, viral transmission of a disease) and those in which each is a consequence of a common cause (such as contact with a non-infective agency possessing some carcinogenic effect). The second part of the study was concerned with the analysis of other epidemiological data in an attempt to shed some light on the factors responsible for the unusual space-time patterns. There seemed to be some evidence that children who developed cancer relatively late and were involved in close pairs (group 2) did not experience infectious

diseases to the same extent as their matched controls, but this did not seem to be true of similar children who were not members of close pairs. The question is, could a lack of pre-onset infections have any cluster significance? Hewitt⁸ has shown that the frequency and timing of measles in children who develop cancer relatively late is compatible with the idea that an attack of measles, among other things, may act as a cancer promoting agent in a susceptible subject. On this two stage model, the promoting agent fails to produce the disease if exposure to it occurs before the child has been made susceptible by the action of some initiating agent. On this basis, one would expect periods in the history of older children during which they experienced less exposure to promoting agents than their matched healthy controls—otherwise their onsets would not have been delayed until relatively late. Data from group 2 in the present study support the view that the common infectious diseases of childhood may play some part in cancer promotion among children who have already become susceptible by other means. If this were so, then one might expect the space-time patterns of the promoting agents to be reproduced on a much reduced scale in the subsequent distribution of cancer cases. This might also explain why clustering has sometimes been reported around nuclear plants or in new towns⁹ since the influx of new people into a geographically isolated area would be associated with increased exposure among the indigenous population to common viral infections. It is interesting to note that Gardner *et al*¹⁰ found no excess of childhood cancers among children attending schools in Seascale who had been born elsewhere, although there was an excess among similar children born and educated in the area.² This would be consistent with the existence of an initiating agent in early life to which incoming children had not been exposed.

I would like to thank Dr Alice Stewart for her help and criticism during the late 1960s when this work was undertaken in Oxford and Dr J. A. H. Waterhouse who allowed me access to the records of the Regional Cancer Registry in Birmingham.

The study was funded by the Goodger Scholarship from the University of Oxford.

- Black D. Investigation of the possible increased incidence of cancer in west Cumbria. Report of independent advisory group, chaired by Sir Douglas Black. London: HMSO, 1984.
- Gardner MJ, Hall AJ, Downes S, Terrell JD. Follow up study of children born to mothers resident in Seascale, West Cumbria (birth cohort). *Br Med J* 1987; 295: 822-7.
- Heasman MA, Kemp IW, Urquhart JD, Black R. Childhood leukaemia in northern Scotland. *Lancet* 1986; i: 266.
- Urquhart J, Cutler J, Burke M. Leukaemia and lymphatic cancer in young people near nuclear installations. *Lancet* 1986; i: 384.
- Knox EG. Epidemiology of childhood leukaemia in Northumberland and Durham. *Br J Prev Soc Med* 1964; 18: 17-24.
- David FN, Barton DE. Two space-time interaction tests for epidemicity. *Br J Prev Soc Med* 1966; 20: 44-8.
- Barton DE, David FN, Merrington M. A criterion for testing contagion in time and space. *Ann Hum Genet* 1965; 29: 97-102.
- Hewitt D. Epidemiological detection of agents whose effects depend on host susceptibility. *J Chron Dis* 1966; 19: 1059-66.
- Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet* 1988; ii: 1323-6.
- Gardner MJ, Hall AJ, Downes S, Terrell JD. Follow up study of children born elsewhere but attending schools in Seascale, West Cumbria (schools cohort). *Br Med J* 1987; 295: 819-22.