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Aggregation of childhood leukemia in geographic areas of Greece

Eleni Petridou, Freda E. Alexander, Dimitrios Trichopoulos, Katharine Revinthi, Nick Dessypris, Naomi Wray, Stavros Haidas, Dimitrios Koliouskas, Helen Kosmidis, Fani Piperopoulou, and Fotini Tzortzatou

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A total of 872 children aged up to 14 years, who were diagnosed with leukemia in Greece during the decade 1980-89, were allocated by place of residence to the 601 administrative districts of the country. Evaluation of spatial clustering was done using the Potthoff-Whittinghill method, which validly assesses heterogeneity of leukemia risk among districts with variable expected numbers of cases. There was highly significant evidence for spatial clustering occurring particularly among children living in urban and, to a lesser extent, semi-urban areas. The evidence was stronger for children younger than 10 years old, applied also to children in different five-year age groups, and persisted when cases of acute lymphoblastic leukemia were analyzed separately. These findings provide support to the hypothesis that localized environmental exposures could contribute to the etiology of childhood leukemia, but they cannot distinguish between exposures of physical or chemical nature, nor can they exclude socially conditioned patterns of exposure to infectious agents. *Cancer Causes and Control* 1997, 8, 239-245

Key words: Childhood leukemia, environmental exposure, Greece, spatial clustering.

Introduction

Spatial clustering can facilitate the study of disease etiology in two ways: first, by documenting the operation of non-random factors in determining the geographic distribution of the disease under consideration; and second, by linking geographic clusters to suspected relevant exposures. With respect to childhood leukemia, these exposures may be population mixing and the associated disturbance of herd immunity,[1,2] specific viral exposures,[3] or environmental pollutants of physical or chemical nature.[4] In contrast to space-time clustering, spatial clustering assumes that the factor(s) responsible for clustering has remained in the same areas for a substantial part of the study period.

An investigation of spatial clustering may be done following the identification of an apparent cluster with or without specification of the suspected exposure; or it

Dr Petridou, Ms Revinthi, and Mr Dessypris are with Department of Hygiene and Epidemiology, Athens University Medical School, Athens, Greece. Authors are also affiliated with the Dept. of Epidemiology, Harvard School of Public Health, Boston, MA, USA (Drs Trichopoulos, Petridou); the Dept. of Public Health Sciences, University of Edinburgh Medical School, Edinburgh, UK (Drs Alexander, Wray); the Dept. of Pediatric Hematology-Oncology, Ag. Sophia Children's Hospital, Athens, Greece (Dr Haidas); the Dept. of Pediatric Hematology- Oncology, Ippocrateion General Hospital, Salonica, Greece (Dr Koliouskas); the Dept. of Pediatric Hematology-Oncology, A. Kyriakou Children's Hospital, Athens, Greece (Dr Kosmidis); the Second Dept. of Pediatrics, Aristoteleion University of Salonica AHEPA General Hospital, Salonica, Greece (Dr Piperopoulou); and the First Dept. of Pediatrics, Athens University Medical School Ag. Sophia Children's Hospital, Athens, Greece (Dr Tzortzatou). Address correspondence to Dr Petridou, Dept. of Hygiene and Epidemiology, Athens University Medical School, 75 M. Asias Str., T.K. 115 27, Athens, Greece. *This project was supported in part by a grant from the Europe Against Cancer Program.*

may be undertaken in order to ascertain whether spatial clustering occurs more frequently than could be expected by chance alone. The second approach has the advantage of being free from the possible biases and other problems associated with the *post hoc* definition of geographic boundaries and can prepare the ground for a systematic effort to identify factors the presence, frequency, or intensity of which may vary concomitantly with the degree of observed clustering.[4]

Most studies concerning clustering of childhood leukemia have focused on space-time clustering because the viral etiology of this disease has been the dominant hypothesis, and viruses, like other infectious agents, can vary simultaneously in time and space.[3] Among studies that have examined spatial clustering, most were undertaken in response to the identification of an apparent cluster,[5,6] whereas others were done in order to evaluate specific etiologic hypotheses.[1,7] Although these studies are valuable, they face problems associated with the arbitrary definition of cluster boundaries.[8-10]

We have evaluated whether cases of childhood leukemia tend to form spatial clusters by studying the 872 cases that occurred during the 10-year period 1980-89 in all 601 administrative districts of Greece. The urban areas of Greece are characterized by intense population mixing due to internal migration, whereas mountainous rural areas are relatively isolated as well as economically less developed.

Materials and methods

Children with leukemia who were diagnosed in Greece during the decade 1 January 1980 to 31 December 1989 were identified through a detailed search of hospital archives throughout Greece by a nationwide team of collaborating childhood oncologists.[11-13] A total of 872 incident cases were identified; gender, age, type of leukemia, date of diagnosis, and parental residence at the time of diagnosis were available for all. These data are reasonably reliable, as it is most unlikely for a child in Greece to be treated for leukemia without involvement of a pediatric oncologist, and all these professionals have contributed to the network that conducted the study.[12] The data were scrutinized to ensure that 'parental residence' had the same interpretation for the case series and for the routinely generated data.

Greece is divided into 601 districts on the basis of geographic location and degree of urbanization. Thus, large metropolitan areas are divided into several districts, whereas several small villages are usually aggregated into one district. Districts adjacent to towns of more than 10,000 inhabitants are considered urban; districts composed of towns with populations between 2,000 and 9,999 inhabitants are considered semi-urban; districts composed of several villages each with fewer than 2,000 inhabitants are considered rural. For every district, the mid-period childhood population was estimated on the basis of data provided by the National Statistical Service of Greece; these data are gender-specific and refer to age groups 0-4, 5-9, and 10-14 years. The expected number of cases in each district is calculated on the basis of the gender- and age-specific person-years at risk and a set of standard rates, adjusted by a multiplicative constant that forces the sum of all expected values to equal the sum of observed cases. Thus, if the total of expected cases is 16.4 and the total of observed cases 15, all expected values are multiplied by 15/16.4.

When spatial clustering for leukemia was evaluated in specific age groups (0-4, 5-9, or 10-14) or the analysis was restricted to cases of acute lymphoblastic leukemia (ALL), different adjustment factors were used. The adjustment factor is, as a rule, different for districts with different degrees of urbanization (urban, semi-urban, rural). This is necessary when the incidence of leukemia differs between urban and rural areas because this difference creates an apparent spatial clustering (in urban or rural areas in general). To facilitate comparisons with results from similar studies that could be undertaken in other European countries rates for total Europe were used as the standard.[14]

Evaluation of spatial clustering was done using the Potthoff-Whittinghill (P-W) method.[15,16] The null hypothesis states that the number of cases in every district is drawn from the same Poisson distribution with variance in every district equal to the respective mean which reflects the district-specific person-years at risk. The P-W alternative hypothesis is that variation between districts is greater than expected from the Poisson distribution after accounting for the different person-time at risk. The P-W test statistic (PW) is the sum over all districts under consideration of the product of observed cases multiplied by observed cases minus one and divided by the expected number of cases in that district. This statistic is compared with its expectation which equals the total number of observed cases minus one. The variance σ^2 of PW is

$$\frac{2\,(m-1)\,E\,(PW)}{(O_+)}$$

where m is the number of districts, $E(PW)$ is the expectation of the P-W test statistic and O_+ is the total number of observed cases. Statistical testing is based on the values of the approximate standardized normal deviance $Z = [PW-E(PW)]/\sigma$. This approach is based on a large numbers' approximation and requires large O_+ and m; this condition certainly is satisfied when all districts and the corresponding leukemia cases are considered collectively, but the approximation is less satisfactory in sub-group

analyses that involve small numbers.

One-sided tests have been used throughout, since a distribution which is more uniform than predicted by Poisson variability is attributed to chance. This is standard practice when spatial clustering is evaluated. Analyses are reported separately for the whole country and for urban and rural areas. The analyses for the whole country do not adjust for observed differences in incidence rates among the three types of area so that these will contribute to any observed extra-Poisson variation.

In order to estimate the strength of the extra-Poisson variation we used a specific model[17] for the variance of the case counts:

$$\text{variance } (O_i) = E_i + \beta E_i$$

where O_i and E_i are the observed and expected counts in the i'th area. Then $\beta = 0$ corresponds to Poisson variability and $\beta > 0$ to extra-Poisson variability and β is estimated by:

$$\hat{\beta} = 2[PW\text{-}E(PW)] / \sigma^2.$$

The standard error of $\hat{\beta}$ is $2/\sigma$. Then $\hat{\beta}$ /SE($\hat{\beta}$) is identical to the Potthoff-Whittinghill Z-statistic. For this reason and since we only consider values of $\beta \geq 0$ to be meaningful, 90 percent confidence intervals (CI) for $\hat{\beta}$ have been provided. This approach has been extended as suggested by Muirhead and Butland.[17] The components of the variance of O_i may be distinguished:

$$\text{variance } (O_i) = E_i + \beta_w E_i + (\beta - \beta_w) E_i$$

where $\beta_w E_i$ is the variance component attributable to aggregation *within* smaller subgroups. This has been applied to specific age-bands (0-4, 5-9, 10-14 years) so that β_w considers clustering in which children of the same age have tended to aggregate in certain small areas and (β - β_w) estimates the extent to which proximity of cases from different age-bands contributes to the overall clustering. It also has been applied in the present analysis to clarify the clustering which has been found in the urban areas; many cities are represented by just a single small area, but each of 15 cities includes more than one small area. For these, β_w can represent clustering *within* the cities, whereas β - β_w is heterogeneity between the cities. The estimator of β_w for the age-group analysis is

$$\hat{\beta}_w = \frac{\sum [PW\ (age) - E(PW\ (age))]}{(m-1) \sum (O_+\ (age) - 1)\ O_+\ (age)}$$

where the summation is over the age groups and

$$SE\ (\hat{\beta}_w) = \sqrt{2 / \sum (m-1)(O_+\ (age) - 1) / O_+\ (age)}\ .$$

Corresponding formulae with obvious modifications apply to the within, and between, city analyses.

Results

Table 1 shows the incidence of childhood leukemia per 10^6 person-years over a 10-year period by type of leukemia, gender, age, and residence at diagnosis.[12] The patterns are not unlike those found in other populations: most leukemia cases are of the acute lymphoblastic type; the incidence of the disease is higher among boys than among girls; there is a clear early childhood peak; and the disease is generally higher in urban than in rural areas, with the semi-urban areas occupying an intermediate position.

Table 2 assesses spatial clustering of childhood leukemia in Greece during the 10-year period 1980-89 using the P-W procedure. In this table, the results for total Greece over all childhood years are highly significant; however, this finding could be a simple reflection of the higher incidence of childhood leukemia in urban rather than rural districts ('urban clustering'). Examination of spatial clustering among districts classified as urban, semi-urban, or rural is not affected by differences in the incidence of childhood leukemia by urban, semi-urban, or rural status since these analyses condition on the total observed numbers in each stratum. Spatial clustering is evident among urban and semi-urban districts, but not in rural areas. When the age groups were considered separately, the strength of the clustering, in both urban and semi-urban districts, was higher for 0-4 years than 5-9 years. The 10-14 year age data showed no evidence of extra-Poisson variation. Table 3 indicates that ALL generates a pattern similar to that for all childhood leukemias, although the strength is slightly weaker. Separate examination of other childhood leukemias for evidence of spatial clustering through the P-W procedure is not appropriate because data are sparse.

Table 4 gives estimates of the extra-Poisson variation parameter for clustering within age bands (*i.e.*, within 0-4 years, 5-9 years, 10-14 years, assuming one parameter applies for these three). These analyses are not applied for the group of rural areas since no evidence of clustering was seen there. In general, the between-age-group component of extra-Poisson variation (β - β_w) is stronger and statistically significant, or approaching significance. These data indicate that case aggregations within small areas tend to involve cases from more than one age stratum.

The results for the urban areas are difficult to interpret. Fifteen cities contain at least two small areas. For these, the overall strength of clustering is almost identical to that for all urban areas. However, this can be attributed

Table 1. Distribution of 872 cases of childhood leukemia by type of leukemia, age, gender, residence at diagnosis and incidence rates per 1,000,000 person-years (Greece, 1980-89)[a]

Area	Gender	Age (yrs)	Type of leukemia					
			Acute lymphoblastic (ALL)		Other type		Total	
			Number	Incidence	Number	Incidence	Number	Incidence
Urban (10,000+ inhabitants)	Boys	0-4	145	65.9	20	9.1	165	75.0
		5-9	89	40.3	11	5.0	100	45.3
		10-14	38	16.9	12	5.3	50	22.2
	Girls	0-4	118	56.5	19	9.1	137	65.6
		5-9	71	33.9	15	7.2	86	41.1
		10-14	25	11.7	10	4.7	35	16.4
Semi-urban (2,000-9,999 inhabitants)	Boys	0-4	22	45.3	5	10.3	27	55.6
		5-9	27	55.2	2	4.1	29	59.3
		10-14	10	19.7	4	7.9	14	27.6
	Girls	0-4	19	42.5	3	6.7	22	49.2
		5-9	12	26.2	1	2.2	13	28.4
		10-14	7	14.9	0	0.0	7	14.9
Rural (< 2,000 inhabitants)	Boys	0-4	43	42.2	2	2.0	45	44.2
		5-9	20	18.9	6	5.7	26	24.6
		10-14	19	17.0	10	9.0	29	26.0
	Girls	0-4	45	46.4	5	5.2	50	51.6
		5-9	20	19.9	4	4.0	24	23.9
		10-14	9	8.5	4	3.8	13	12.3
Total	Boys	0-4	210	56.7	27	7.3	237	64.0
		5-9	136	36.2	19	5.1	155	41.3
		10-14	67	17.3	26	6.7	93	24.0
	Girls	0-4	182	52.0	27	7.7	209	59.7
		5-9	103	28.9	20	5.6	123	34.5
		10-14	41	11.2	14	3.8	55	15.0

[a] Ref. 12.

to variation between small areas – within cities, since the estimate of the strength for the within-city component of extra-Poisson variation is generally larger. It remains somewhat doubtful whether this should be referred to as 'clustering.' Much of this heterogeneity is generated by extremely high incidence rates in the 10 'small' areas which are the largest (*e.g.*, central Athens is a single 'small' area containing 94 of the 872 cases).

Discussion

Examination of spatial clustering of diseases is an intuitively appealing way of studying disease etiology but it has not been particularly fruitful in identifying causes of chronic diseases, including cancer.[6] There are several reasons for this failure. *Post hoc* examination of clusters is hampered by the inability to evaluate accurately the role of chance through standard statistical procedures.[4] Moreover, the long latency of many chronic diseases, movements of population at risk, and mobility of infectious organisms (if these are indeed etiologic agents) reduce the statistical power of tests evaluating spatial clustering. Combination of these problems has led to many nonproductive investigations[6,18,19] and, occasionally, to misleading conclusions.[9,10]

Recently, a number of tests that do not depend on setting arbitrary boundaries have been proposed[20-23] but they are complex or computationally demanding. A test proposed several years ago by Potthoff and Whittinghill[15,16] evaluates heterogeneity of disease risk among geographic regions with built-in adjustment for variability in size of population at risk. We have decided to use this test on theoretical grounds before any examination of the data, because the test does not depend on setting arbitrary boundaries, is computationally simple, and is sufficiently powerful against the specified alternative. Other suitable statistical procedures have not been applied in these data, and we cannot comment on their relative performance.

We have used the Potthoff-Whittinghill test to evaluate spatial clustering of childhood leukemia across the 601 administrative districts of Greece with stratification by five-year age groups, urban, semi-urban, or rural residence, and leukemia type (acute lymphoblastic, other).

Table 2. Evaluation of the place clustering of childhood leukemia in Greece, 1980-89, through the Potthoff-Whittinghill (PW) test

	All ages	0-4 yrs	5-9 yrs	10-14 yrs
Urban districts (n = 169)				
Observed PW	626.5	333.2	207.7	76.5
Expected PW	572	301	185	84
Z[a]	2.98	1.76	1.24	-0.41
P-value	0.001	0.04	0.11	—
$\hat{\beta}$ [b]	0.32	0.19	0.14	-0.41
(CI)[c]	(0.14-0.50)	(0.01-0.37)	(-0.04-0.32)	(-0.20-0.16)
Semi-urban districts (n = 286)				
Observed PW	170.4	88.8	65.1	14.1
Expected PW	111	48	41	20
Z[a]	2.5	1.73	1.02	-0.25
P-value	0.006	0.04	0.15	—
$\hat{\beta}$ [b]	0.21	0.15	0.09	-0.02
(CI)[c]	(0.07-0.35)	(0.01-0.29)	(-0.05-0.23)	(-0.16-0.12)
Rural (n = 148)				
Observed PW	176.5	86.3	39.7	56.3
Expected PW	186	94	49	41
Z[a]	-0.55	-0.45	-0.55	0.90
P-value	—	—	—	0.18
$\hat{\beta}$ [b]	-0.06	-0.05	-0.06	0.11
(CI)[c]	(-0.26-0.12)	(-0.25-0.14)	(-0.25-0.13)	(-0.09-0.31)
All areas (n = 603)				
Observed PW	1001.25	521.4	337.6	146.5
Expected PW	871	445	277	147
Z[a]	3.76	2.20	1.75	-0.01
P-value	0.0001	0.01	0.04	—
$\hat{\beta}$ [b]	0.22	0.13	0.10	-0.0008
(CI)[c]	(0.13-0.31)	(0.035-0.22)	(0.006-0.20)	(-0.09-0.09)

[a] $Z = [PW - E(PW)]/\sigma$.
[b] $\hat{\beta} = 2[PW - E(PW)]/\sigma$.
[c] CI = 90% confidence interval.

Our data indicate that spatial clustering is evident in urban and also in semi-urban areas and it is limited largely to children less than 10 years old. It is evident also for ALL alone. These results should be contrasted with those from a place-time clustering analysis of the same data[12] in which clustering was evident only for leukemia cases among children less than five years old.

Space-time clustering suggests an etiology involving exposure to infectious agents followed by a short, or relatively constant latent period. Spatial clustering may be attributable either to fixed environmental sources or to infectious agents – especially agents causing prolonged or repeated epidemics in single areas or involving variable latent periods. The combined results can be interpreted readily as either evidence that childhood leukemia aggregations, especially beyond the childhood peak, may be influenced by fixed environmental sources or as further evidence of an infectious etiology with longer and more variable latent periods applicable to the older cases.

Whereas many studies have examined real or perceived clusters with or without reference to a suspected cause,[3,18,19] few investigations have attempted to document the existence of clusters to an extent incompatible with chance expectation.[23-25] Most of these studies did observe a tendency of spatial clustering and, in some investigations,[24-25] the authors have proposed data derived etiologic hypotheses – notably, population density[25] or use of fossil fuels.[24] It appears that spatial clustering may be a genuine phenomenon in childhood leukemia but the factors generating the clustering remain elusive. It is possible that intense population mixing in dense urban centers of population groups with variable levels of herd immunity would explain the observed pattern of spatial clustering. However, generation of clusters from localized sources of chemical or physical nature cannot be excluded. A study is now in progress[26] to assess whether the degree of spatial clustering tends to co-vary with the likelihood of exposure to factors or conditions that have been

Table 3. Evaluation of the place clustering of acute lymphoblastic leukemia in Greece, 1980-89, through the Potthoff-Whittinghill (PW) test

	All ages	0-4 yrs	5-9 yrs	10-14 yrs
Urban districts (n = 169)				
Observed PW	528.5	301.4	184.4	53.3
Expected PW	485	262	159	62
Z[a]	2.38	2.15	1.39	-0.48
P-value	0.01	0.02	0.08	—
$\hat{\beta}$ [b]	0.26	0.24	0.15	-0.05
(CI)[c]	(0.08-0.44)	(0.06-0.42)	(-0.03-0.33)	(-0.23-0.13)
Semi-urban districts (n = 286)				
Observed PW	147.1	65.9	60.5	17.4
Expected PW	96	40	38	16
Z[a]	2.15	1.04	0.95	0.06
P-value	0.02	0.15	0.17	0.48
$\hat{\beta}$ [b]	0.18	0.09	0.08	0.005
(CI)[c]	(0.04-0.32)	(-0.05-0.23)	(-0.06-0.22)	(-0.14-0.15)
Rural (n = 148)				
Observed PW	135.4	80.4	30.9	8.5
Expected PW	155	87	39	27
Z[a]	-1.15	-0.39	-0.48	-1.10
P-value	—	—	—	—
$\hat{\beta}$ [b]	-0.13	-0.05	-0.06	-0.13
(CI)[c]	(-0.33-0.06)	(-0.23-0.15)	(-0.25-0.13)	(-0.32-0.06)
All areas (n = 603)				
Observed PW	839.5	458.8	304.4	82.1
Expected PW	738	391	238	107
Z[a]	2.93	1.96	1.92	-0.72
P-value	0.002	0.02	0.03	—
$\hat{\beta}$ [b]	0.17	0.11	0.11	-0.04
(CI)[c]	(0.08-0.26)	(0.02-0.21)	(0.02-0.20)	(-0.13-0.05)

[a] $Z = (PW - E[PW])/\sigma$.
[b] $\hat{\beta} = 2[PW - E(PW)]/\sigma$.
[c] CI = 90% confidence interval.

Table 4. Magnitude of within and between age-group clustering effects, Greece

	District type		
	Urban	Semi-urban	All areas
Total leukemia			
Within age-groups ($\hat{\beta}_w$)	0.095	0.071	0.076
(CI)[a]	(-0.009-0.20)	(-0.01-0.15)	(0.02-0.13)
Between age-groups ($\hat{\beta} - \hat{\beta}_w$)	0.225	0.14	0.14
(CI)[a]	(0.02-0.43)	(-0.02-0.30)	(0.03-0.25)
ALL[b]			
Within age-groups ($\hat{\beta}_w$)	0.11	0.06	0.06
(CI)[a]	(0.008-0.22)	(-0.02-0.14)	(0.005-0.11)
Between age-groups ($\hat{\beta} - \hat{\beta}_w$)	0.15	0.12	0.11
(CI)[a]	(-0.06-0.36)	(-0.03-0.28)	(0-0.22)

[a] CI = 90% confidence interval.
[b] ALL = acute lymphoblastic leukemia.

proposed to be linked causally to childhood leukemia, including population mixing,[1] population density,[25] and extremely-low-frequency electromagnetic fields.[27]

The finding in this study that spatial clustering was more evident in large cities is intriguing but needs to be interpreted with caution, particularly in view of the British data in which any evidence for spatial clustering was restricted to sparsely populated areas.[28] It is certainly possible for certain aspects of herd immunity and specific physical or chemical pollutants to have dissimilar spatial distribution patterns in different countries. However, independent evidence is needed for singling out a particular exposure as more relevant and for dispelling residual concerns about methodologic artifacts.

References

1. Kinlen L, Clarke K, Hudson C. Evidence from population mixing in British New Towns 1946-85 of an infective basis for childhood leukaemia. *Lancet* 1990; 336: 577-82.
2. Kinlen LJ, Petridou E. Childhood leukemia and rural population movements in Greece, Italy, and other countries. *Cancer Causes Control* 1995; 6: 445-50.
3. Alexander FE. Viruses, clusters and clustering of childhood leukaemia: a new prospective? *Eur J Cancer* 1993; 29: 1424-43.
4. MacMahon B, Trichopoulos D. *Epidemiology: Principles and Methods. 2nd Edition*. Boston, MA (USA): Little Brown and Co. 1996.
5. Heath CW Jr, Hasterlik RJ. Leukemia among children in a suburban community. *Am J Med* 1963; 34: 796-812.
6. Rothman KJ. A sobering start for the cluster busters' conference. *Am J Epidemiol* 1990; 132: S6-13.
7. Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J* 1990; 300 : 423-9.
8. Beral V. Childhood leukemia near nuclear plants in the United Kingdom: the evolution of a systematic approach to studying rare disease in small geographical areas. *Am J Epidemiol* 1990; 132: S63-8.
9. MacMahon B. Leukemia clusters around nuclear facilities in Britain. *Cancer Causes Control* 1992; 3: 283-8.
10. Doll R, Evans HJ, Darby SC. Paternal exposure not to blame. *Nature* 1994; 367: 678-80.
11. Kassimos D. The epidemiology of childhood leukemia in Greece. Doctoral dissertation. Athens University Medical School, Athens, Greece. 1992.
12. Petridou E, Revinthi K, Alexander F, *et al*. Space-time clustering of childhood leukaemia in Greece: evidence supporting a viral aetiology. *Br J Cancer* 1996; 73: 1278-83.
13. Petridou E, Trichopoulos D, Dessypris N, *et al*. Infant leukaemia after in utero exposure to radiation from Chernobyl. *Nature* 1996; 382: 352-3.
14. Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL, eds. *International Incidence of Childhood Cancer.* Lyon, France: International Agency for Research on Cancer, 1988; IARC Sci. Pub. No. 87.
15. Potthoff R, Whittinghill M. Testing for homogeneity: The binomial and multinomial distributions. *Biometrika* 1966; 53: 167-82.
16. Potthoff R, Whittinghill M. Testing for homogeneity: The Poisson distribution. *Biometrika* 1966; 53: 183-90.
17. Muirhead CR, Butland BK. Testing for over-dispersion using an adapted form of the Potthoff-Whittinghill method. In: Alexander FE, Boyle P, eds. *Methods of Investigating Localized Clustering of Disease.* Lyon, France: International Agency for Research on Cancer, 1996; IARC Sci. Pub. No. 135.
18. Caldwell GG. Twenty-two years of cancer cluster investigations at the Centers for Disease Control. *Am J Epidemiol* 1990; 132: S43-7.
19. Centers for Disease Control. Proceedings of the National Conference on Clustering of Health Events, 1989. *Am J Epidemiol* 1990; 132(Suppl).
20. Cuzick J, Edwards R. Spatial clustering for inhomogeneous populations. *J R Stat Soc [B]* 1990; 52: 73-104.
21. Turnbull BW, Iwano EJ, Burnett WS, Howe HL, Clark LC. Statistical Considerations – Theory. Monitoring for clusters of disease: application to leukemia incidence in upstate New York. *Am J Epidemiol* 1990; 132: S136-43.
22. Jacquez GM. Cuzick and Edwards' test when exact location are unknown. *Am J Epidemiol* 1994; 140: 58-64.
23. Openshaw S, Craft AW, Charlton M, Birch J.M. Investigation of leukemia clusters by use of a geographical analysis machine. *Lancet* 1988; 1: 272-3.
24. Knox EG. Leukaemia clusters in childhood: geographical analysis in Britain. *J Epidemiol Comm Health* 1994; 48: 369-76.
25. Muirhead CR. Childhood leukemia in metropolitan regions in the United States: a possible relation to population density? *Cancer Causes Control* 1995; 6: 383-8.
26. Alexander FE, Wray N, Boyle P, *et al*. Clustering of childhood leukaemia: a European study in progress. *J Epidemiol Biostat* 1996; 1: 13-22.
27. Washburn EP, Orza MJ, Berlin JA, *et al*. Residential proximity to electricity transmission and distribution equipment and risk of childhood leukemia, childhood lymphoma, and childhood nervous system tumors: systematic review, evaluation and meta-analysis. *Cancer Causes Control* 1994; 5: 299-309.
28. Draper GJ. The geographical epidemiology of childhood leukaemia and non-Hodgkin lymphoma in Great Britain, 1966-1983. London, UK: HMSO, 1990.