



**HAL**  
open science

## Spatial clustering and space-time clusters of leukemia among children in Germany, 1987-2007

Sven Schmiedel, Maria Blettner, Peter Kaatsch, Joachim Schüz

► **To cite this version:**

Sven Schmiedel, Maria Blettner, Peter Kaatsch, Joachim Schüz. Spatial clustering and space-time clusters of leukemia among children in Germany, 1987-2007. *European Journal of Epidemiology*, 2010, 25 (9), pp.627-633. 10.1007/s10654-010-9488-7. hal-00607697

**HAL Id: hal-00607697**

**<https://hal.science/hal-00607697>**

Submitted on 11 Jul 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Title: Spatial clustering and space–time clusters of leukemia among children in Germany, 1987–2007**

Schmiedel, Sven<sup>1,2</sup>; Blettner, Maria<sup>2</sup>; Kaatsch, Peter<sup>3</sup>; Schüz, Joachim<sup>1</sup>

1 Institute for Cancer Epidemiology, Danish Cancer Society, Strandboulevarden 49, 2300 Copenhagen, Denmark

2 Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Centre of the Johannes Gutenberg-University Mainz, 55101 Mainz, Germany

3 German Childhood Cancer Registry, Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Centre of the Johannes Gutenberg-University Mainz, 55101 Mainz, Germany

Corresponding author:

Sven Schmiedel

Institute for Medical Biostatistics, Epidemiology and Informatics

University Medical Centre of the Johannes Gutenberg-University Mainz

55101 Mainz

Germany

Phone: +49/6131/173232

Fax: +49/6131/172968

Email: sven@cancer.dk

Abstract (189 words)

Leukemia is the most frequent malignancy in children under the age of 15 years. The question of whether childhood leukemia has a tendency for clustering or forms clusters has been studied for several decades. The environmental risk factor discussed most often is infection, which might result in spatial clustering and space-time clusters. The German Childhood Cancer Registry provided data on 11 946 children with leukemia diagnosed during 1987–2007, as classified in the International Classification for Childhood Cancer (third edition), aggregated by municipality. We used the Potthoff-Whittinghill model to test for a general trend for clustering and the spatial scan statistic to search for localized clusters. No evidence of global clustering was found, neither for the whole study population nor in sub-groups by age, period or population density, or for different types of leukemia. A similar result was found for localized clusters. The analysis shows no evidence of a tendency to clustering, however, aggregation of data at the municipality level might have diluted small localized clusters. The results of this study do not provide support for the hypothesis of an infectious or a spatial environmental etiology of childhood leukemia.

Key words: leukemia, children, clustering, spatial, Germany

Abbreviations:

ALL: acute lymphoblastic leukemia

AML: acute myeloblastic leukemia

COMARE Committee on Medical Aspects of Radiation in the Environment

ICCC: International Classification of Childhood Cancer

CI: Confidence interval

## Introduction

Leukemia is the most frequent malignancy in children under the age of 15 years, with an incidence rate of 5.2 per 100 000 children per year in Germany during 1998–2007. It is a disease of early childhood, with a distinct peak in incidence rate between the ages of 2 and 5 years. The major morphological groups of childhood leukemia are acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) [1]. The question whether childhood leukemia has a tendency to cluster has been studied for more than 70 years [2].

It is important to distinguish between ‘clusters’ and ‘clustering’. Whereas a cluster emerges in a small defined area and therefore consists of only a few cases, clustering involves the overall propensity of cases to form clusters. Furthermore, statistical tests on clusters and clustering can be classified as ‘focused’ or ‘general’. A focused test covers the inclusion area around predefined foci, whereas a general test is of the overall pattern in a study area [3].

In the early twentieth century, ALL was thought to be an infectious disease [4], and clusters were interpreted as providing supporting evidence for this hypothesis. Whether infections play a causal role in leukemogenesis is still unclear. There are currently three hypotheses on the role of infections in the etiology of childhood leukemia. (1) Kinlen’s hypothesis is based on an unusual type of population mixing in isolated areas with low population density [5]. He proposed that the transiently higher rates of childhood leukemia follows this type of population mixing, which leads to infections in previously unexposed susceptible children by infected newcomers. Leukemia of any kind in both populations would be a rare outcome as a reaction to yet-unknown but mild infectious agents and reflects the immune naivety in both populations. (2) Greaves’ ‘delayed-infection’ hypothesis sought to explain the peak

incidence of common B-cell precursor ALL in children aged 2–5 years by proposing infections as a crucial second factor in the context of the ‘two-hit model’ of Knudson, which postulates that cancer is the result of at least two mutations (hits) to a cell’s DNA [6]. Greaves’ hypothesis postulates an aberrant response to infections as a second necessary ‘hit’ after lack of exposure to infectious agents during infancy and subsequent failure of modulation of the child’s immune system [1]. (3) Smith’s hypothesis places the second essential hit during pregnancy, and not during infancy [7]. The causative agent induces an infection in a pregnant woman, and the infection is then transferred to the fetus and increases the child’s risk for ALL before the age of 5 years. All three hypotheses claim a possible role for infections in the etiology of leukemia. If a general trend towards spatial clustering was observed the hypothesis of an infectious etiology of childhood leukemia would be strengthened. If space-time clusters would be detected this would be more in line with the hypothesis of Kinlen.

Since 1990, there have been to our knowledge 15 peer-reviewed publications on studies of clusters, spatial clustering or space-time interaction of childhood leukemia in different countries, in different age groups and with the use of various statistical methods. Ten had their focus on clusters [8, 9, 10] and spatial clustering [11, 12, 13, 14, 15, 16, 17], two on space-time interaction alone [18, 19]. Three studies investigated both [20, 21, 22]. Four found no spatial clustering and clusters at all [8-11], four found statistically significant results for at least one subgroup [14, 16, 21, 22], and five found spatial clustering for the overall group of leukemia [12, 13, 15, 17, 20]. The five studies which investigated space-time interaction all found statistically significant results [18, 19, 20, 21, 22]. However, in the explorative approach of Bellec et al. [22] 140 Knox tests were carried out, which leads to problems due to multiple testing.

In summary there is no clear evidence for or against spatial clustering. It is remarkable that most of the studies conducted in the UK show a trend towards spatial clustering, especially in the age group of the incidence peak of childhood leukemia of ages 2 to 5 years and also for ALL, in line with the infectious hypotheses (see above). The populations in these studies partially overlap, and the results are therefore not independent. The most comprehensive study from the UK is summarized in the eleventh report of Committee on Medical Aspects of Radiation in the Environment (COMARE) and here a trend for spatial clustering was found, although the effect was small [23]. Studies in other countries show a more diverse picture, although the use of various methods makes direct comparison difficult. The largest study to date, which included more than 13 000 children in several mainly European countries, the so-called EUROCLUS project, showed a statistically significant trend to spatial clustering, although, again, the trend was weak [15]. For a detailed review, see McNally and Eden [24].

As infections and most of the environmental agents possibly related to the risk of childhood leukemia, like ionizing radiation due to domestic exposure to radon [25], air pollutants [26] or pesticides [27], are spatially heterogeneously distributed, it is conceivable that childhood leukemia also shows a tendency to spatial clustering with a temporal component. Thus, spatial and space–time analysis of the distribution of childhood leukemia might give a hint to environmental agent(s), possibly infections, which are involved in the etiology of the disease.

Our study on clustering of leukemia in Germany is based on data from the German Childhood Cancer Registry, covering a population of approximately 13.2 million children aged 0–14 years per year. The presence of clusters and clustering was investigated at municipality level.

## Material and Methods

### Cases

We included all children up to the age of 14 years with primary leukemia diagnosed in the period 1987–2007 and registered in the German Childhood Cancer Registry, yielding 11 946 cases. We excluded 36 cases (0.3%) as they were either anonymized ( $n = 9$ ) or information on the municipality of residence at the time of diagnosis was missing ( $n = 27$ ). The German Childhood Cancer Registry is estimated to be at least 95% complete [28,29]. Cases are coded according to the International Classification of Childhood Cancer, third edition (ICCC-3) [30]. Contrary to earlier versions of the ICCC, myeloproliferative diseases are now part of the first class, 'Leukemias, myeloproliferative and myelodysplastic diseases', of the ICCC-3, which has been in use at the registry since 2006. Actually 2.9% of the cases have these diseases which represent preleukemic stages. Furthermore, the two subgroups separately analyzed in the result section include only cases with leukemia (ALL and AML). Data from the former German Democratic Republic have been included in the registry since 1991, i.e. shortly after the reunification of Germany.

### Study population

Germany consists of 12 500 administrative units, of which 238 are not inhabited, leaving 12 262 inhabited areas with a total of 82 217 658 inhabitants on an area of 353 044.1 km<sup>2</sup>. Children under the age of 15 years represent 13.7 % of the inhabitants of Germany (all data are for 31 December 2007, from Bundesamt für Kartografie und Geodäsie, Statistisches Bundesamt).

The average population under 15 years in the municipalities ranged from 1 to 438 554 (data on inhabitants in each municipality of each year of the study period 1987-2007 were collected from the statistical offices of each Federal state, for the

federal states of the former German Democratic Republic for the years 1991-2007). Children under 15 years accounted for on average fewer than 1 000 inhabitants in 9 847 municipalities (80.3 %), for 1 000–10 000 in 2 286 municipalities (18.6 %), for 10 000–100 000 in 125 municipalities (1.0 %) and for > 100 000 in four municipalities (0.03 %). Therefore the expected number of cases in the municipalities varied from  $3.3 \times 10^{-4}$  to 437. Latter is found in Berlin which is a single administrative unit, which has more than 3.4 million inhabitants.

### Statistical methods

Usually, a binomial distribution with parameter  $p$  of the chance for being a case in a population of size  $n$  should be used for incidence data aggregated at municipality level. As for rare diseases like childhood leukemia  $p$  is very small and  $n$  is usually very large, a Poisson distribution with intensity parameter  $\lambda = n p$  can be used as an approximation of the binomial distribution. The major assumption of Poisson distribution is the equality of variance and mean. A greater variance than the mean is called 'overdispersion', which is associated with heterogeneity in the data and hence with clustering. The Q statistic is obtained by dividing the empirical variance by the empirical mean [31]; if the observed cases follow a Poisson distribution, the mean and the variance should be equal and the statistic should be close to 1. This method was used in a previous investigation of clustering with data from the German Childhood Cancer Registry [9]. The major drawback of this test is that it does not include the number of inhabitants in each municipality. Therefore, municipalities were classified into 100 groups by the number of expected cases to make the variation in the groups comparable.

The Potthoff-Whittinghill statistic is more often used and tests for spatial heterogeneity or a trend for clustering. Under the null hypothesis, the number of



cases in each municipality follows a Poisson distribution, as explained above. The alternative to overdispersion is described by a negative binomial, for which the variance of the mean ratio is  $1 + \beta$  [32-34]. This method expresses overdispersion in relation to the mean by a single parameter  $\beta$ , and  $\beta = 0$  is tested in a score test.

Analyses were conducted overall and in subgroups by age (0–4, 5–9, 10–14 years), by morphology (all leukemia, ALL, AML) and by time period (1987–1997, 1998–2007). R software was used for analysis [35].

The Pothoff-Whittinghill method disregards spatial relations among municipalities. In order to use this additional information, the Kulldorff spatial scan statistic was also used for investigating clusters [36]. This method involves drawing all possible circles in the study region with municipalities' centroids as the centers and determining whether there were more cases inside the circle than expected. The most likely cluster is found by a likelihood ratio test. This method can be expanded to include the time dimension (space–time cluster), whereby the two-dimensional circles drawn in the area can be interpreted as cylinders in a three-dimensional version. We used this approach in order to find space-time clusters. SaTScan software was used for the Kulldorff spatial scan statistic [37].

## Results

Table 1 shows the distribution of the leukemia cases by diagnostic subgroup, as defined by the ICCC-3.

Figure 1 shows the mean and the variance for each of the 100 groups of municipalities based on increasing number of expected cases. The scatter plot covers only 96 of the 100 groups, as three groups were omitted as no cases were observed, and the group with the largest number of expected cases was excluded as its variance was an outlier owing to large differences in the number of inhabitants. The figure shows that the variance and the mean are close in each group, indicating that the observed cases per municipality follow a Poisson distribution. The variance was greater than the mean only in the last group, due to greater variation in the numbers of children in the largest cities of Germany.

The  $Q$  statistic confirms this observation. If the observed cases follow a Poisson distribution, the statistic is expected to be 1. The minimum of the statistic for groups 1–99 was 0.74 and the maximum was 1.81; and for three of these 99 groups, a  $Q$  statistic could not be calculated, as no cases were observed. For group 100, the variance was large (72.73), because of the large variation in the number of inhabitants in the municipalities in this group. If  $Q$  is greater than 1, this indicates a tendency to overdispersion. This would be expected for half of the groups due to chance; however, this was the case in only 36 of the 97 groups studied.

The score test based on the Potthoff-Whittinghill model (Table 2) showed no statistically significant results overall or for any of the subgroups. Furthermore, classification into former German Democratic Republic (East Germany) and former Federal Republic of Germany (West Germany) and into municipalities with low population density ( $< 50$  persons per  $50 \text{ km}^2$ ) did not alter this overall result.

The municipalities were also aggregated into 459 units in order to achieve equal area size ( $900 \text{ km}^2$ , which is the area of Berlin, Figure 2). The result based on these 459

units was not statistically significant for overall childhood leukemia ( $\beta = -0.057$ ,  $SE(\beta) = 0.066$ ,  $p$  value = 0.77, not calculated for subgroups).

Using the spatial scan statistic (Table 3) we did not find evidence for clusters, neither overall nor in any of the subgroups. This was true for both the purely spatial and for the space-time analysis.

## Discussion

This study is based on a large data set from an international highly reputed cancer registry. With 11 946 cases of childhood leukemia, it is one of the largest investigations of spatial clustering of childhood leukemia. None of the analyses showed any evidence for a general tendency to clustering of cases of childhood leukemia. Neither localized clusters nor a tendency to spatial clustering were found in the data. Further, the results of analyses of subgroups by age, morphologic type of leukemia and study period were in line with this overall finding; in particular, there was no evidence of clustering of ALL cases or of cases in children aged 2–5 years, two subgroups of a priori interest on the basis of previous research.

The findings of the present study are in contrast to those of the EUROCLUS project [20], in which significant evidence for clustering of all leukemia was found in small administrative units in Europe ( $p = 0.03$ ). In a recent publication from the UK [22], the authors reported a statistically significant result for overdispersion, providing evidence for spatial clustering for all leukemia and ALL, although the effects were small (overall:  $\beta = 0.045$  (90 % CI: 0.02; 0.07), ALL:  $\beta = 0.05$  (90 % CI: 0.025; 0.07)).

There are several possible explanations for these contrasting results. One is that the smallest administrative unit in the United Kingdom, a 'ward', usually has about 6 000 inhabitants. Therefore, any variation in environmental exposure within each administrative unit is likely to be small. In Germany, administrative units vary from those containing only a few people to metropolitan areas like Berlin, with more than 3 million people. Areas with few inhabitants, and therefore with no or one case, are to contribute no information to the statistic based on the Potthoff-Whittinghill model. In cities with many inhabitants, the variations in exposure may be too great to reveal clustering across the city. The last problem cannot be addressed, i.e. large cities cannot be subdivided into smaller units, but small municipalities can be aggregated to obtain areas with larger numbers. This was done by laying a grid with a pixel size of 900 km<sup>2</sup> (size of Berlin) over a map of Germany and combining the municipalities with centroids in each grid, resulting in 459 artificially created areas (Figure 2). The result of the test did not, however, change the overall finding of no clustering.

Our results are in line with those of a study in France [16]; however, French administrative units show similar diversity in the numbers of inhabitants to that in Germany.

By using the approach of Potthoff-Whittinghill, a test with reasonable statistical power in a variety of overdispersion models was chosen [33]. It is an appropriate approach to find a general trend of clustering, but not appropriate to locate specific clusters. To locate specific clusters we used the spatial scan statistic as complimentary approach. This approach has most statistical power in detecting localized clusters appearing in a circular shape [38] in a variety of different assumptions of clusters in urban, rural or mixed settings. This method was also used finding space-time clusters; however, no statistically significant results were found.

Strengths of our study are the large sample size, the long observation period and the virtually complete case ascertainment based on an established population-based cancer registry. Moreover, the denominator for the calculations, i.e. the population sizes in each municipality, is highly accurate due to the German system of compulsory resident registration. One limitation of our study is that it is based on data aggregated at municipality level. This might have diluted any effect in two ways. First, clustering might occur across the borders between municipalities. This would be blurred by the arbitrariness of the demarcation and therefore could not be identified. Secondly, it is possible that clustering exists within large municipalities, which have a large number of inhabitants, and hence cannot be discerned.

At first glance, our findings appear to be in contrast to the statistically significant results of a German study that showed a decreasing risk for childhood leukemia by distance from a nuclear power plant [39, 40]. There are two possible explanations for this. First, clusters around the nuclear power plants may be too small to be found at the aggregated municipality level used in this study. Secondly, it is possible that local investigation of a cluster leads to statistically significant results, even though it is still in the range of expectation at the global (or national) scale.

The results of this study do not provide support for the hypothesis of an infectious etiology of childhood leukemia. The clusters found with the spatial scan statistic were not statistically significant. However, it might be that in an albeit large, still relatively homogeneous population like that of Germany, the amount of contact with infectious agents depends more on the individual than on the area, so that no strong space–time effect is to be expected.

Analysis in the whole of Germany over a 20-year period showed no evidence for a tendency for clustering of childhood leukemia. Thus, although localized clusters

might exist and be significant, these might be in the expected range of the global pattern. The results of our study do not provide support for the hypothesis of a spatial environmental factor or an infectious etiology of leukemia in children.

### Acknowledgements

The authors would like to thank Claudia Spix and Irene Jung at the German Childhood Cancer Registry for extracting data. We also thank Jørgen Olsen and Finn Diderichsen for the support and Richard Feltbower for the useful discussion on methodology. Sven Schmiedel is supported by an international PhD stipend from the The Danish Strategic Research Council (grant number 645-06-0479).

## References

1. Greaves M. Science, medicine, and the future: childhood leukaemia. *BMJ* 2002;324: 283–287.
2. Kellett CE. Acute myeloid leukaemia in one of identical twins. *Arch Dis Child* 1937;12: 239–252.
3. Besag J, Newell J. The detection of clusters in rare diseases. *J R Stat Soc Ser A* 1991;154:143–155.
4. Ward G. The infective theory of acute leukaemia. *Br J Child Dis* 1917;24: 10–20
5. Kinlen LJ. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet* 1988;ii:1323–1327.
6. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA* 1971;68: 820–823.
7. Smith M. Considerations on a possible viral etiology for B-precursor acute lymphoblastic leukemia of childhood. *J Immunother* 1997;20: 89–100.
8. Muir KR, Parkes SE, Mann JR, Stevens MC, Cameron AH, Raafat F, Darbyshire PJ, Ingram DR, Davis A, Gascoigne D. Clustering—real or apparent? Probability maps of childhood cancer in the West Midlands Health Authority Region. *Int J Epidemiol* 1990;19: 853–859.
9. Hjalmars U, Kulldorff M, Gustafsson G, Nagarwalla N. Childhood leukaemia in Sweden: using GIS and a spatial scan statistic for cluster detection. *Stat Med* 1996;15: 707–715.

10. Mosavi-Jarrahi A, Moini M, Mohagheghi MA, Alebouyeh M, Yazdizadeh B, Shahabian A, Nahvijo A, Alizadeh R. Clustering of childhood cancer in the inner city of Tehran metropolitan area: a GIS-based analysis. *Int J Hyg Environ Health* 2007; 210: 113–119.
11. Westermeier T, Michaelis J. Applicability of the Poisson distribution to model the data of the German Children's Cancer Registry. *Radiat Environ Biophys* 1995;34: 7–11.
12. Knox EG, Gilman EA. Spatial clustering of childhood cancers in Great Britain. *J Epidemiol Community Health* 1996;50: 313–319.
13. Petridou E, Alexander FE, Trichopoulos D, Revinthi K, Dessypris N, Wray N, Haidas S, Kolioukas D, Kosmidis H, Piperopoulou F, Tzortzatos F. Aggregation of childhood leukemia in geographic areas of Greece. *Cancer Causes Control* 1997;8: 239–245.
14. Alexander FE, Chan LC, Lam TH, Yuen P, Leung NK, Ha SY, Yuen HL, Li CK, Li CK, Lau YL, Greaves MF. Clustering of childhood leukaemia in Hong Kong: association with the childhood peak and common acute lymphoblastic leukaemia and with population mixing. *Br J Cancer* 1997;75:457–463.
15. Alexander FE, Boyle P, Carli PM, Coebergh JW, Draper GJ, Ekbohm A, Levi F, McKinney PA, McWhirter W, Michaelis J, Peris-Bonet R, Petridou E, Pompe-Kirn V, Plisko I, Pukkala E, Rahu M, Storm H, Terracini B, Vatten L, Wray N. Spatial clustering of childhood leukaemia: summary results from the EUROCLUS project. *Br J Cancer* 1998;77:818–824.



16. Dockerty JD, Sharples KJ, Borman B. An assessment of spatial clustering of leukaemias and lymphomas among young people in New Zealand. *J Epidemiol Community Health* 1999;53: 154–158.
17. McNally RJQ, Alexander FE, Vincent TJ, Murphy MF. Spatial clustering of childhood cancer in Great Britain during the period 1969–1993. *Int J Cancer* 2009;124: 932–936.
18. Gilman EA, Knox EG. Childhood cancers: space–time distribution in Britain. *J Epidemiol Community Health* 1995;49: 158–163.
19. Gustafsson B, Carstensen J. Space–time clustering of childhood lymphatic leukaemias and non-Hodgkin's lymphomas in Sweden. *Eur J Epidemiol* 2000;16: 1111–1116.
20. Birch JM, Alexander FE, Blair V, Eden OB, Taylor GM, McNally RJQ. Space–time clustering patterns in childhood leukaemia support a role for infection. *Br J Cancer* 2000;82: 1571–1576.
21. McNally RJQ, Alexander FE, Birch JM. Space–time clustering analyses of childhood acute lymphoblastic leukaemia by immunophenotype. *Br J Cancer* 2002;87(5): 513–515.
22. Bellec S, Hémon D, Rudant J, Goubin A, Clavel J. Spatial and space–time clustering of childhood acute leukaemia in France from 1990 to 2000: a nationwide study. *Br J Cancer* 2006;94: 763–770.
23. Committee on Medical Aspects of Radiation in the Environment (COMARE) (2006). Eleventh Report. The distribution of childhood leukaemia and other childhood cancer in Great Britain 1969–1993. Health Protection Agency, July 2006.

24. McNally RJQ, Eden TO. An infectious aetiology for childhood acute leukaemia: a review of the evidence. *Br J Haematol* 2004;127: 243–263.
25. Raaschou-Nielsen O. Indoor radon and childhood leukaemia. *Radiat Prot Dosimetry* 2008;132: 175–181.
26. Whitworth KW, Symanski E, Coker AL. Childhood lymphohematopoietic cancer incidence and hazardous air pollutants in southeast Texas, 1995–2004. *Environ Health Perspect* 2008;116: 1576–1580.
27. Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y, Patte C, Pacquement H, Vérité C, Robert A, Michel G, Margueritte G, Gandemer V, Hémon D, Clavel J. Household exposure to pesticides and risk of childhood hematopoietic malignancies: The ESCALE study (SFCE). *Environ Health Perspect* 2007;115: 1787–1793.
28. Kaatsch P, Spix C. German Childhood Cancer Registry. Annual Report 2006/2007. 2007, University Mainz.
29. Steliarova-Foucher E, Kaatsch P, Lacour B, Pompe-Kirn V, Eser S, Miranda A, Danzon A, Ratiu A, Parkin DM. Quality, comparability and methods of analysis of data on childhood cancer in Europe (1978-1997): report from the ACCIS project. *Eur J Cancer* 2006;42:1915-1951.
30. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, Third Edition. *Cancer* 2005;103:1457–67.
31. Fisher RA. The significance of deviations from expectation in a Poisson series. *Biometrics* 1964;20: 265–272

32. Potthoff RF, Whittinghill M. Testing for homogeneity. I. The binomial and multinomial distribution. *Biometrika* 1966a;53: 167–182.
33. Potthoff RF, Whittinghill M. Testing for homogeneity. II. The Poisson distribution. *Biometrika* 1966b;53: 183–190.
34. Muirhead CR. Methods for detecting disease clustering, with consideration of childhood leukaemia. *Stat Meth Med Res* 2006;15: 363–383.
35. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, 2009. ISBN 3900051070, URL <http://www.R-project.org>.
36. Kulldorff M. A spatial scan statistic. *Commun Statist Theory Meth* 1997;26: 1481–1496.
37. Kulldorff M. SatScanTMv5.1: Software for the spatial and space–time scan statistics, Information Management Services 2004 Inc. <http://www.SatScan.org/S>
38. Song C, Kulldorff M. Power evaluation of disease clustering tests. *Int J Health Geogr* 2003;2:9.
39. Kaatsch P, Spix C, Schulze-Rath R, Schmiedel S, Blettner M. Leukaemia in young children living in the vicinity of German nuclear power plants. *Int J Cancer* 2008;122: 721–726.
40. Spix C, Schmiedel S, Kaatsch P, Schulze-Rath R, Blettner M. Case–control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980–2003. *Eur J Cancer* 2008;44: 275–284.

Table 1. Cases of childhood leukemia among children under 15 years in the German Childhood Cancer Registry (1987–2007), classified according to the International Classification of Childhood Cancer, third edition (ICCC-3)

| Classification   | n      | %     |
|--|--------|-------|
| I Leukemia, myeloproliferative and myelodysplastic diseases        | 11 946 | 100.0 |
| I.a Lymphoid leukemia  | 9 638  | 80.7  |
| I.b Acute myeloid leukemia   | 1 642  | 13.7  |
| I.c Chronic myeloproliferative diseases                            | 145    | 1.2   |
| I.d Myelodysplastic syndrome and other myeloproliferative diseases | 417    | 3.5   |
| I.e Unspecified and other specified leukemia                       | 104    | 0.9   |

Table 2. Results of the score test on spatial heterogeneity based on the Potthoff-Whittinghill model for the incidence of childhood leukemia overall, in leukemia subgroups, by population density groups and by east and west Germany, Germany 1987–2003

|               |                                     | Whole study period |  | 1987–1997 |  | 1998–2007 |  |
|---------------|-------------------------------------|--------------------|--|-----------|--|-----------|--|
|               |                                     | No. Cases          | $\beta$ , [SE $\beta$ ], ( <i>p</i> value) | No. cases | $\beta$ , [SE $\beta$ ], ( <i>p</i> value) | No. cases | $\beta$ , [SE $\beta$ ], ( <i>p</i> value) |
| All cases     | 0–14 years                          | 11 946             | –0.000 [0.013] (0.52)                      | 5 832     | 0.005 [0.013] (0.37)                       | 6 114     | 0.000 [0.013] (0.50)                       |
|               | 0–4 years                           | 6 103              | –0.007 [0.013] (0.67)                      |           |  |           |  |
|               | 5–9 years                           | 3 407              | –0.027 [0.013] (0.93)                      |           |  |           |  |
|               | 10–14 years                         | 2 436              | –0.006 [0.013] (0.74)                      |           |  |           |  |
| ALL¶          | 0–14 years                          | 9 638              | 0.003 [0.013] (0.39)                       | 4 779     | 0.010 [0.013] (0.30)                       | 4 859     | 0.007 [0.013] (0.29)                       |
|               | 0–4 years                           | 5 080              | 0.005 [0.013] (0.33)                       |           |  |           |  |
|               | 5–9 years                           | 2 846              | –0.021 [0.013] (0.88)                      |           |  |           |  |
|               | 10–14 years                         | 1 712              | –0.014 [0.013] (0.98)                      |           |  |           |  |
| AML‡          | 0–14 years                          | 1 642              | –0.020 [0.013] (0.77)                      | 833       | –0.018 [0.013] (0.77)                      | 809       | 0.010 [0.013] (0.26)                       |
|               | 0–4 years                           | 760                | –0.018 [0.013] (0.69)                      |           |  |           |  |
|               | 5–9 years                           | 381                | –0.023 [0.013] (0.77)                      |           |  |           |  |
|               | 10–14 years                         | 501                | –0.001 [0.013] (0.43)                      |           |  |           |  |
| All cases     | <50 Inhabitants per km <sup>2</sup> | 360                | 0.017 [0.025] (0.20)                       |           |  |           |  |
|               | >50 Inhabitants per km <sup>2</sup> | 11 586             | –0.005 [0.015] (0.65)                      |           |  |           |  |
| West Germany† |                                     |                    | *  |           |  | 5 332     | 0.004 [0.015] (0.37)                       |
| East Germany† |                                     |                    | *  |           |  | 782       | –0.014 [0.023] (0.64)                      |

¶ acute lymphoblastic leukemia,

‡ acute myeloblastic leukemia,

† West Germany includes the federal states of the former Federal Republic of Germany (Schleswig-Holstein, Hamburg, Lower Saxony, Bremen, North Rhine-Westphalia, Hesse, Rhineland-Palatinate, Saarland, Baden-Württemberg, the Free State of Bavaria, Berlin), East Germany includes the federal states on the territory of the former German Democratic Republic (Mecklenburg-Western Pomerania, Brandenburg, Saxony-Anhalt, the Free State of Thuringia, the Free State of Saxony)

\* was only analysed in the second study phase (1988-2007) as East Germany is included in the registry since 1991

Table 3. Result of use of spatial scan statistic on detection of clusters of childhood leukemia in Germany in the period 1987–2003; purely spatial and space–time analyses

|            |                | 1987–2007  |           |           |             | 1987–1997  | 1998–2007  |
|------------|----------------|------------|-----------|-----------|-------------|------------|------------|
|            |                | 0–14 years | 0–4 years | 5–9 years | 10–14 years | 0–14 years | 0–14 years |
| Spatial    | Radius (km)    | 107.7      | 20.9      | 27.0      | 68.4        | 25.0       | 46.8       |
|            | Observed       | 1092       | 69        | 35        | 170         | 48         | 168        |
|            | Expected       | 956        | 39        | 17        | 120         | 25         | 120        |
|            | <i>p</i> value | 0.28       | 0.39      | 0.91      | 0.25        | 0.54       | 0.57       |
| Space–time | Period*        | 1998–2007  | 1988–1990 | 2003      | 2006–2007   | 1990–1991  | 2005–2007  |
|            | Radius (km)    | 121.3      | 9.6       | 7.1       | 5.8         | 4.4        | 32.4       |
|            | Observed       | 539        | 8         | 3         | 5           | 5          | 53         |
|            | Expected       | 423        | 0.6       | 0.02      | 0.15        | 0.11       | 25         |
|            | <i>p</i> value | 0.15       | 0.32      | 0.72      | 0.56        | 0.09       | 0.70       |

\* Defined by the cluster with the lowest *p* value

## Figure legends

Figure 1. Mean and variance on logarithmic scale for 100 groups formed from 12 262 municipalities sorted by increasing estimated number of cases of childhood leukemia. Group 100, with the largest estimated number of cases, is not included as it is an outlier, because of to varying numbers of inhabitants. The first three groups were also excluded, as no case was observed.

Figure 2. Aggregation of 12 262 German municipalities into 30 x 30 km<sup>2</sup> squares by centring around centroid of the municipality of Berlin (459 areas)





