Epidemiologic Evaluation of Leukemia Incidence in Children and Adults in the Vicinity of the Nuclear Power Plant Krümmel (KKK)

Wolfgang Hoffmann, Eberhard Greiser, Bremen

Abstract

Between February 1990 to the end of 1995 six cases of childhood leukemia were diagnosed among residents of the small rural community Elbmarsch in Northern Germany. Five of these cases were diagnosed in only 16 months between Feb. 1990 and May 1991. The cases all lived in close proximity (500-4500 m) to Germany's largest capacity nuclear boiling water reactor (KKK).

Standardized incidence ratios (SIR) and exact 95% confidence intervals were calculated for a circular area with a 5 km radius around the plant. For the time period 1990 to 1995 the SIR was 464 (208-1034). If the analysis is restricted to the years 1990 and 1991, the SIR increases to 1175 (489-2827).

This cluster of childhood leukemia cases cannot presently be explained in terms of established and putative risk factors for childhood leukemia, including radiation from medical sources.

After this unprecedented childhood leukemia cluster had been detected, it was hypothesized that leukemia incidence could also be increased in adults. To test this hypothesis, a retrospective incidence study was conducted which covered 10 years (1984-1993) and three adjacent counties with a total population of about 470,000. Case ascertainment was done perusing documents of multiple primary data sources including all hospitals, institutes of pathology, oncology centers, as well as practicing physicians and three Departments of Health within the study area and in adjacent counties, respectively. After linking of documents from all sources a total of 1985 verified cases of leukemias, malignant lymphomas and multiple myeloma remained. Incidence rates were standardized to the 1987 West Germany census population structure. Proximity to KKK was operationalized by constructing concentric circles with radii 5 km (10, 15, 20 km) around the site of the plant.

When overall incidence was used as a reference, SIR for leukemia in the 5 km-region was elevated for both genders (observed 51, expected 40; SIR 128; p=0.046), whereas no such elevation was observed in any of the other circles. The increased incidence was attributable to males (SIR 156; p=0.01) and was most pronounced, but not confined to, chronic myeloid leukemia.When the analysis was restricted to persons below age 65, SIR were significantly increased for both males and females. The excess risk observed over the 10 year study period was exclusively due to an increased incidence from 1989 through 1993.

A subsequent case control study including all cases identified in the incidence study is indicated to identify possible causes for the excess leukemia risk for children and adults in the vicinity of KKK.

Introduction

The rural community Elbmarsch is situated on the southern bank of the river Elbe, some 30 km south-east of the City of Hamburg in Lower Saxony. In a population of less than 2000 children under 15 years 6 cases of leukemia were diagnosed since 1990. Five of these cases had occurred in the time period between February 1990 and May 1991. The sixth case was diagnosed recently in 1995. This cluster is hitherto unprecedented in Germany with respect to its temporal and spatial dimension [19]. Though we cannot exclude the existence of a comparable childhood leukemia cluster elsewhere, we are presently unaware of any mentioning in the international literature.

The cases were all living in close vicinity to the nuclear power plant Kernkraftwerk Krümmel (KKK) which is situated at the northern bank of the river Elbe, just opposite of the Elbmarsch. KKK is Germany's largest capacity nuclear boiling water reactor (1300 MWel). It was put into operation in 1984. Adjacent to KKK the nuclear research institute GKSS (Gesellschaft zur Kernenergieverwertung in Schiffbau und Schiffahrt) operates two research reactors of 5 and 15 MW, respectively, since the late 1950s.

This epidemiological situation generated considerable public concern and media coverage. The local authorities reacted promptly: In order to investigate possible causes of the increased incidence of leukemias, the Federal State of Lower Saxony in Feb. 1992 established an interdisciplinary scientific committee, which initially consisted of 25 experts.

Established and suspected risk factors for leukemia include low dose ionizing radiation from natural [11, 43, 57, 59] and man-made sources [54, 60] at all ages (preconceptional [26, 66, 80], prenatal [18, 30, 61, 64], and postnatal [28, 56]), exposure to benzene [1, 6, 50-52], low-frequency electromagnetic fields [23, 76, 91] (see [74, 75, 90] for recent reviews), and pesticides [9, 21, 34, 58, 68]. Despite detailed investigations into the medical, residential, family, social and occupational histories of the afflicted families which were supplemented with extensive physical, chemical, and toxicological analyses, no unusual exposure to any of these factors was detected. The expert committee therefore concluded, that only a detailed epidemiologic study could shed further light on the etiology of the cluster. In order for any epidemiological approach to be sensible, however, both the age range and the area that is being studied needed to be extended. As a first step the expert committee suggested a retrospective incidence study, covering children and adults in the three adjacent rural districts of the Elbmarsch (total population 480,000). The project was assigned to the Bremen Institute for Prevention Research and Social Medicine, where considerable experience was available from earlier studies with similiar questions [33, 35, 36, 45-47].

Tab. 1 The Retrospective Incidence Study Elbmarsch: Design elements

Study area	Rural districts Lüneburg, Harburg (Lower Saxony); Rural district Herzogtum Lauenburg (Schleswig-Holstein) Total population 480.000
Target diagnoses	Leukemia (all forms), malignant lymphoma, multiple myeloma, related diseases and syndromes
Inclusion criteria	Residence in study area at time of 1st diagnosis, German citizenship
Age groups	all ages (children, adults)
Study period	1984 - 1993
Methods	Active case ascertainment, compilation of multiple primary data sources

Materials and Methods

Design

Princpal design of the study presented herein is a retrospective geographical incidence analysis. The most important design features are summarized in Tab. 1.

Case ascertainment and data sources

Fundamental requirement for any geographical incidence study is the complete ascertainment of all incident cases alike over all single years of the study period and in all regions of the study area.

Whereas this task is trivial in countries in which central cancer registries exist, it becomes particularly tedious in countries without established registration. In Germany only childhood cancers are routinely registered in a central cancer registry [55].

Hence case ascertainment needed to resort to the vast array of primary data sources. Among the sources analysed were the patient documentation and medical history file archives of all hospitals in the study area, the pathologic and cytologic institutes which cover the study area with respect to tissue samples and biopsies, and the private practices of all General Practitioners and a number of other specialties in the study area. Since patients with target diseases are often referred to University Hospitals, specialized clinics, or treatment facilities, several sources outside the study area were included. Finally all death certificates for the study period and area were abstracted in the respective Departments of Health (Tab. 2). Wherever available, secondary sources (discharge books, laboratory protocols, referral books, nurses' notes etc.) were also completely screened for candidate cases. Any hint was validated thoroughly, however cases were only accepted if the secondary data could be confirmed in the medical history or any equivalent written document.

Altogether some 2.5 million files were analysed for this study.

Tab. 2 Primary data sources

Hospitals in study area	**8**
Hospitals in adjacent rural districts and regional centers	**14** *)
- Departments	46
Hematology/Oncology	4
Internal Medicine	15
Pediatrics	3
Pathology	8
Radiation therapy	6
Surgery	7
Computer tomography	2
Ear, nose, throat	1
Private practices	**314**
- Specialities	
General Practitioners	223
Internal Medicine/Oncology	63
Pediatrics	28
Regional oncological clinics	**3**
Dept. of Health	**3**

*) Including Medical Universities: Kiel, Lübeck, Hamburg (UKE)

Record linkage

All cases were subsequently compared by various dimensions (Date of birth, sex, diagnosis, date of first diagnosis, rural commune of residence) to link the datasets of those patients who had been abstracted from more than one data source. As a consequence of the complete screening of all available data sources some 60% of the patients had been documented in at least two independent sources (not counting different data sources within the same department or hospital).

The first stages of the record linkage were always performed while the screening in various primary and secondary data sources and departments of the same hospital was still ongoing. Most discrepancies could thus be resolved and many incomplete datasets could still be supplemented by specific investigations with full access to the original data.

Remaining inconsistencies and unconfirmed cases could in some cases be solved and completed in the final step of the record linkage process, in which the data from all sources were compiled.

Standardized incidence ratios

As a measure for the geographical incidence pattern standardized incidence ratios (SIR) were calculated. SIR reflect the ratio between an observed (age-)standardized incidence and a reference incidence. An SIR of 100 indicates that the standardized incidences in the region of interest is the same as in the reference population. An SIR below 100 means a lower standardized incidence in the region of interest, an SIR above 100 corresponds to an increased standardized incidence in the region of interest.

P-values were calculated for all SIR under the assumption of a Poisson distribution [7] to quantify the probability that an observed increase in incidence is actually due to chance. In line with the general convention, statistical significance is assumed if this probability is less than 0.05. In the results section of this paper approximated confidence intervals are given in addition to the p-values. Unlike the p-values, these confidence intervals are based on rounded SIR. The purpose of these intervals is visualization of the differential precision of single values in the figures. They should not be interpreted in terms of statistical significance.

Reference population

The most desirable reference population in a geographical incidence study would be the general population of the Federal Republic of Germany as a whole. However, incidence data on the national level do not exist in Germany. In Federal State of Saarland incidences have routinely been published for each year after 1972, but due to considerable differences with respect to population density, industrialization and other factors we assume that the figures do not readily apply to the population in Northern Germany.

To avoid systematic under- or overestimation of the expected incidence in the study area, we selected as the reference the overall incidence in the pooled population of the study region. Indirect age standardization for both the incidences in the regions of interest and the reference was performed applying the age-specific incidences to the population of the Federal Republic of Germany, as determined in the national census of 1987.

Hypothesis

In principle, an incidence study can be done for purely descriptive purposes and hence does not necessarily require an a priori hypothesis. However, the circumstances under which the Retrospective Incidence Study Elbmarsch was commissioned clearly implied a geographical analysis with respect to the nuclear power plant Krümmel and the GKSS. It was to be determined, whether or not an increase in leukemia incidence, which had been observed in children in the direct vicinity of the nuclear facilities would also be present in adults. To allow for analysis of a trend with distance, concentric regions of 0-5, 5-10, 10-15, 15-20 and more than 20 km around the facilities were constructed.

The second purpose of the study was to derive SIR for each of the 35 administrative units of the study area („incidence mapping"; results not presented).

Results

For the years 1984-1993 4600 cases with target diseases were abstracted from the primary data sources. After extensive record linkage 2253 distinct cases remained.
In 261 of these information on the year of primary diagnosis was insufficient or completely absent. The majority of these cases had been abstracted from death certificates which in Germany do not routinely contain this information. To avoid any possible overestimation of the SIR, all 261 were excluded from the analysis, although a major proportion of these cases had likely been diagnosed in the study period. Another seven cases were documented with typical monoclonal gammopathy, but the diagnosis of multiple myeloma could not be substantiated before the study was closed. These cases were also excluded.
Consequently, the analysis was based on 1985 cases (Table 3).

Leukemias

Main result of the analysis was a statistically significant increase in the incidence of leukemia (all forms) for both sexes combined in the 0-5 km-region around the plant. Between 1984 and 1992 51 cases were observed, whereas only 40 cases would have been expected. The (age-)standardized incidence exceeded the overall age-standardized incidence in the study area by 28 % (SIR=128; p=0,046, Fig. 1).
No significant deviations from the expected values were observed in any of the remaining concentric regions for both sexes combined and in separate analyses for males and females. The gender specific analyses, however, revealed that the excess incidence in the vicinity of the plant was confined to males (32 cases observed, 21 expected; SIR = 156; p=0.0099; Fig. 1).

Chronic myeloid leukemia

Chronic myeloid leukemia (CML) accounted for about half of the excess cases in the 0-5 km region. In a subgroup analysis the SIR for CML was 194 for both sexes combined (p = 0.049), the excess again being attributable to excess cases in males (obs. 10, exp. 5.4; SIR = 275; p=0.013; Fig. 2).

Tab. 3 Distribution of cases over diagnostic groups and subgroups

Diagnoses	Males	Females	Total
Leukemias (all forms)	338	295	**633**
Major subgroups:			
- acute leukemia	133	99	**232**
- other leukemia	205	196	**401**
Subtypes:			
- CML	48	37	**85**
- CLL	137	135	**272**
NHL	321	274	**595**
M.Hodgkin	91	66	**157**
Mult. myeloma	142	175	**317**
Myeloproliferative syndrome/ myelodysplastic syndrome	115	139	**254**
Aplastic anemia	8	21	**29**
Total	**1015**	**970**	**1985**

CML = chronic myloid leukemia; CLL = chronic lymphatic leukemia; NHL = Non Hodgkin's lymphoma; Mult myeloma = multiple myeloma

Age distribution of the SIR

In another subgroup analysis, cases were dichotomized according to their ages at the time of first diagnosis. When age 65 is used as a cutpoint roughly half of the patients end up in the younger age group.

The results of the cases below 65 years show a different pattern as was observed for all age groups combined. Again, incidence of all leukemias was found significantly increased in the central region (obs. 31, exp. 16.8; SIR=178; p=0.0023). However, unlike in the previous analysis for all ages combined, amog the younger cases both males and females contributed to this increase to a comparable extent. About half of the excess cases under 65 years of age were males (obs. 17, exp. 9.8; SIR=65.6; p = 0.041) and females, respectively (obs. 14, exp. 7; SIR=194.4; p=0.013; Fig. 3). This pattern was similiar in separate analyses for the agegroups 0-<15 and 15-64 years (results not shown).

Comparison of SIR in 1984-1988 vs. 1989-1993

To evaluate any temporal trend in leukemia incidence in the vicinity of the nuclear power plant the study period was divided into two consecutive 5 year periods, 1984-1988 and 1989-1993, respectively. The excess in leukemia incidence in the 0-5 km region for both genders combined was confined almost exclusively to the more recent 5 year period (obs. 30, exp. 19.3; SIR=155; p=0.015), whereas between 1984-1988 no deviation from the expected value was observed (21 obs., 21.1 exp.). The increased incidence in the 0-5 km region in 1989-1992 again was mostly attributable to excess cases in males (obs. 18, exp. 10.1; SIR=180; p=0.016), but SIR were also elevated in females (obs. 8, exp. 5.5; SIR=127.3), though this elevation was not statistically significant (p>0.2).

Discussion

„Cluster" analysis has become a widely used term for the study of spatial disease patterns in small geographical areas [15]. Though by definition ecological at the design level, many small area studies have been supplemented with investigations at the individual level. Cluster analysis then developes into „micro-epidemiology" [71]. While micro-epidemiology has been criticized for its conceptual and methodological limitations [72, 73], some well-known examples nevertheless prove its principal potential as a tool in environmental epidemiology [2, 13, 44, 67, 78].

Results of cluster analysis and micro-epidemiology have become key arguments in a debate on childhood and juvenile leukemia risks in the vicinity of nuclear facilities (see [25, 62, 81, 89] for reviews). Increased risks were observed in geographical studies in England and Wales [3-5, 12, 22, 24, 27, 70, 84, 85], Scotland [41, 42, 48], the US [10, 14, 31, 32, 40, 53], Germany [17, 37, 38, 46, 63, 69] and recently in France [86-88].

Hardly ever, however, have detailed geographical leukemia incidence studies included adults of all ages. This is likely due to both methodological difficulties and the tremendous endeavour of a complete case ascertainment in terms of time and cost.

In the Southeastern Massachusetts Health Study, all leukemias except CLL were ascertained among adults over a period of three years in five towns adjacent to the nuclear boiling water reactor Pilgrim near Portsmouth, Massachusetts (USA). Data sources were vital statistics records and the Massachusetts cancer registry. Using statewide incidences as a reference, the SIR for all leukemias (except CLL) was 160 (27 obs., 16.9 exp.; 95% confidence interval 108-237) [10]. In a subgroup analysis, also the SIR for myelogenous leukemias was significantly increased (19 obs., 9.9 exp.; SIR=191; 95%CI 120-304). As in our study, the increase was confined to males (13 obs., 5 exp.; SIR 252).

In a subsequent case control study including 115 leukemia cases and 230 healthy controls, information on individual risk factors like smoking, socioeconomic factors, and occupational exposures were obtained by means of standardized telephone interviews and the analyses were adjusted for each of these factors simultaneously. A composite exposure index was then calculated using distance of residence and place of work to the plant, weighted with the time spent at each location and the total time the respective locations were downwind of the plant. When levels of this exposure index were trichotomized, and the lowest third was used as a reference, resulting odds ratios increased from 2.2 (95%CI 0.9-5.2) for males and 1.5 (0.4-5.6) for females in the medium third to 3.12 (1.2-8.5) and 6.5 (1.53-27.2) for males and females, respectively in the highest exposure category [65].

Radioactive exposure

The childhood leukemia cluster in the 0-5 km region immediately suggests a potential role of radioactive releases of KKK and/or GKSS. However, careful examination of protocols of the routine environmental radiation surveillance around the nuclear facilities yielded no indication for any major accidental release. Radioactive contamination of lifestock, soil, and vegetation with long-lived radionuclides was in the range which was usually observed in Northern Germany after the Chernobyl catastrophy. Whole-body counting of Elbmarsch inhabitants in 1991 likewise yielded moderately elevated specific activities of incorporated Caesium-137 which could be attributed to the Chernobyl fallout.

Many authors have stressed that exposure doses in the vicinity of nuclear power plants in normal operation are several orders of magnitude too small to cause any somatic effect [16, 20, 39, 65].

Discussing a potential contribution of radioactive releases of the plants in quantitative terms, however, it should be taken into account that

- the susceptibility for radiation-induced leukemia increases with younger age by a factor of 5-10 (adults vs. children below age 5 [79]). When prenatal exposure is considered this ratio comes close to 100 [82].
- preconceptional exposure adds a comparatively new exposure pathway which is still not accounted for in conventional risk coefficients [66, 80]. The magnitude of this effect is presently unknown.
- effects of complex combinations of environmental exposures are still very poorly understood. Nevertheless, synergistic effects between radiation and other, e.g. chemical exposures could well enhance the leukemogenic potential of either of the factors [29, 92].

Finally, exposure assessment in such studies is usually considerably less than perfect. Routine environmental radiation surveillance can miss exposures due to *- and ß-emitters or extremely inhomogenous spatial/temporal distributions of raadionuclides. Indeed, we havespeculated earlier [77] that elevated rates of structural chromosomal aberrations in a casual sample of Elbmarsch residents would be compatible with past releases of short-lived fission products which could have been missed by routine surveillance.

Some of the subgroup results are well in line with the radiation hypothesis. For all leukemias, the increase in SIR was highest in children, but, to a lesser degree was also present in adults. CML, which was also significantly increased in both sexes and in males, is a sentinel radiation-induced leukemia. The fact that the increase in incidence began only after 1989, whereas no such elevation was observed for the years 1984-1988 could correspond to the commissioning of the nuclear power plant in 1984. A minimum latency period of 5 years for radiation induced leukemia is compatible to the findings in the survivors of Hiroshima and Nagasaki [8] as well as in the Oxford Survey of Childhood Cancer [83]. The maximum of the latency distribution for adults, however, is considerably later than 5 years [49]. Hence, if the increase in leukemia incidence in the 0-5 km region would indeed be radiation-induced this would imply that the bulk of excess adult cases is still to come, even if the radioactive exposure was confined to the early years of operation of the plant.

At this point geographical epidemiology cannot provide any further insight. The abundance of investigations and measurements which have so far been performed can be condensed into just a few causal hypotheses, which now must be tested in analytical studies. For this purpose a large case-control study is presently being designed and will probably be commissioned by the Federal Ministry for the Environment, Natural Protection and Reactor Safety in early 1996.

Conclusion

An increased leukemia incidence in adults was observed in the 0-5 km region around the nuclear boiling water reactor Krümmel and the nuclear research facility GKSS, an area where a hitherto unprecedented childhood leukemia cluster had been confirmed earlier.

It cannot be stressed enough, though, that due to the ecologic character of the Retrospective Incidence Study Elbmarsch the findings must not be interpreted in terms of causality. So far, the association between an increased incidence of leukemia and the immediate vicinity of the nuclear reactor Krümmel is merely geographical.

However, main results of this study as well as findings in subgroup analyses are compatible with a contribution of the nuclear facilities to the excess cases:

- a significant increase in leukemia incidence in the 0-5 km region around the nuclear power plant, for both genders combined and males only (1984-1993), together with expected incidences in all other geographical regions.
- a significant increase in chronic myeloid leukemia in both genders and males only (1984-1993)
- significantly elevated SIRs for leukemia in males and females below 65 years of age (1984-1992)
- appearance of excess cases only after 1989 whereas incidences were as expected in the first 5 years of the operation of the plant.

These results clearly require further investigations into the possible causes for this unique cluster of childhood and adult leukemia. Most appropriately this could be done by means of an epidemiologic case-control study.

References

1. Aksoy M, Erdem S. Follow-up study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic exposure to benzene. Blood 1978;52:285-292.
2. Baris YI, Simonato L, Artvinli M, et al. Epidemiology and environmental evidence of health effects of exposure to erionite: A four year study. International Journal of Cancer 1987;39:10-17.
3. Baron JA. Cancer mortality in small areas around nuclear facilities in England and Wales. Br J Cancer 1984;50:815-824.
4. Barton CJ, Roman E, Ryder HM, Watson A. Childhood leukemia in West Berkshire [letter]. Lancet 1985:1248-1249.
5. Black D. Investigation of the possible increased incidence of cancer in West Cumbria: Report of the Independent Advisory Group. London Her Majesty's Stationary Office, 1984.

6. Brandt L, Nilsson PG, Mitelman F. Occupational exposure to petroleum products in men with acute non-lymphatocytic leukaemia. BMJ 1978;4:553.

7. Breslow NE, Day NE. Statistical methods in cancer research. Vol. II - The design and analysis of cohort studies. Lyon IARC, 1987.

8. Brill AB, Tomonaga M, Heyssel RM. Leukemia in man following exposure to ionizing radiation. Ann Intern Med 1962;56(4):590-609.

9. Brown LM, Blair A, Gibson R, et al. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res 1990;50:6585-6591.

10. Clapp R, Cobb S, Chan C, Walker B. Leukemia near Massachusetts nuclear power plant [letter]. Lancet 1987;2:1324-1325.

11. Collmann GW, Loomis DP, Sandler DP. Childhood cancer mortality and radon concentration in drinking water in North Carolina. Br J Cancer 1991;63:626-629.

12. Cook-Mozaffari PJ, Darby SC, Doll R, et al. Geographical variation in mortality from leukemia and other cancers in England and Wales in relation to proximity to nuclear installations, 1969-78. Br J Cancer 1989;59:476-485.

13. Creech J, Johnson MN. Angiosarcoma of the liver in the manufacture of polyvinyl chloride. J Occup Med 1974;16:150-151.

14. Crump KS, Ng T-H, Cuddihy RG. Cancer incidence patterns in the Denver metropolitan area in relation to the Rocky Flats Plant. Am J Epidemiol 1987;126:127-135.

15. Cuzick J, Elliott P. Small-area studies: Purpose and methods. In: Elliott P, Cuzick J, English D, Stern R, editors. Geographical and Environmental Epidemiology. Oxford, New York, Tokyo: Oxford University Press, 1992:14.

16. Darby SC, Doll R. Fallout, radiation doses near Dounreay, and childhood leukaemia. BMJ 1987;294:603-607.

17. Demuth M. Leukämieerkrankungen bei Kindern in der Umgebung von Atomanlagen. In: Köhnlein W, Kuni H, Schmitz-Feuerhake I, editors. Niedrigdosisstrahlung und Gesundheit. Berlin: Springer Verlag, 1990:127-35.

18. Diamond EL, Schmerler H, Lilienfeld AM. The relationship of intra-uterine radiation to subsequent mortality and development of leukemia in children. Am J Epidemiol 1973;97:283-313.

19. Dieckmann H. Häufung von Leukämieerkrankungen in der Elbmarsch. Gesundheitswesen 1992;10:592-596.

20. Dionian J, Wan SL, Wrixon AD. Radiation doses to members of the public around AWRE, Aldermaston, ROF, Burghfield and AERE, Harwell. Chilton, Didcot, Oxon National Radiation Protection Board, 1987.

21. Epstein S, Ozonoff D. Leukemias and blood dyscrasias following exposure to Chlordane and Heptachlor. Teratogenesis Carcinog Mutagen 1987;7:527-540.

22. Ewings PD, Bowies C, Phillips MJ, Johnson SAN. Incidence of leukemia in young people in the vicinity of Hinkley Point nuclear power station, 1959-1986. BMJ 1989;299:289-293.

23. Feychting M, Ahlborn A. Magnetic fields and cancer in people residing near Swedish high-voltage power lines. Am J Epidemiol 1993;138:467-481.

24. Forman D, Cook-Mozaffari P, Darby S, et al. Cancer near nuclear installations. Nature 1987;329:499-505.

25. Gardner MJ. Review of reported increases of childhood cancer rates in the vicinity of nuclear installations in the UK. Journal of the Royal Statistical Society A 1989;152:307-325.

26. Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of a case-control study of leukemia and lymphoma among young people near Sellafied nuclear plant in West Cumbria. BMJ 1990;300:423-442.

27. Gardner MJ, Winter PD. Mortality in Cumberland during 1959-1978 with reference to cancer in young people around Windscale [letter]. Lancet 1984:217-218.

28. Gibson RS, Graham S, Lilienfeld A, Schuman L, Dowd JE, Levin ML. Irradiation in the epidemiology of leukemia among adults. JNCI 1972;48:301-311.

29. Gibson RW, Bross IDJ, Graham S, et al. Leukemia in children exposed to multiple risk factors. N Engl J Med 1968;279(17):906-909.

30. Gilman EA, Kneale GW, Knox EG, Stewart A. Pregnancy and childhood cancers: Effects of exposure age and radiation dose. J Radiol Prot 1988;8(1):3-8.

31. Goldsmith JR. Childhood leukemia mortality before 1970 among populations near two US nuclear installations [letter]. Lancet 1989;1:793.
32. Goldsmith JR. Childhood leukemia mortality before 1970 among populations near two US nuclear installations. Lancet 1989;2:1443-1444.
33. Greiser E, Lotz I. Leukämie-Inzidenz in der Nähe einer Sondermülldeponie. Bremen Bremer Institut für Präventionsforschung, 1990.
34. Greiser E, Lotz I, Hoffmann W, Schill W, Hilbig K. Nähe zu einer Sondermülldeponie und andere Risikofaktoren für die Entstehung von Leukämien, malignen Lymphomen und multiplen Myelomen. Bremen, Germany Bremer Institut für Präventionsforschung (BIPS), 1995.
35. Greiser E, Lotz I, Hoffmann W, Wosniok W. Leukämien, maligne Lymphome und Multiple Myelome im Landkreis Holzminden. Orientierende Einschätzung der epidemiologischen Situation unter besonderer Berücksichtigung der Gemeinde Bevern. Bremen Bremer Institut für Präventionsforschung und Sozialmedizin (BIPS), 1994.
36. Greiser E, Lotz I, Steinkohl M, Brand H. Leukämien und maligne Lymphome in den niedersächsischen Landkreisen Nienburg und Schaumburg - Regionale Inzidenzen in 24 Gemeinden. Bremen Bremer Institut für Präventionsforschung, 1991.
37. Grosche B, Hinz G, Tsavachidis C, Kaul A. Analyse der Leukämiemorbidität in Bayern in den Jahren 1976-1981. Teil I Grundlagen, Methodik und medizinische Aspekte. Neuherberg Bayerisches Staatsministerium für Landesentwicklung und Umweltfragen (Hrsg.), Institut für Strahlenhygiene des Bundesgesundheitsamtes, 1987.
38. Grosche B, Hinz G, Tsavachidis C, Kaul A. Analyse der Leukämiemorbidität in Bayern in den Jahren 1976-1981. Teil II. Risikofaktoren, regionale Verteilung und epidemiologische Aspekte. Neuherberg Bayerisches Staatsministerium für Landesentwicklung und Umweltfragen (Hrsg.), Institut für Strahlenhygiene des Bundesgesundheitsamtes, 1987.
39. Hatch MC, Beyea J, Nieves JW, Susser M. Cancer near the Three Mile Island nuclear plant: Radiation emissions. Am J Epidemiol 1990;132(3):397-412.
40. Hatch MC, Wallenstein S, Beyea J, Nieves JW, Susser M. Cancer rates after the Three Mile Island nuclear accident and proximity of residence to the plant. Am J Public Health 1991;81(6):719-724.
41. Heasman MA, Kemp IW, MacLaren A, Trotter P, Gillis CR, Hole AJ. Incidence of leukemia in young persons in the West of Scotland [letter]. Lancet 1984;1:1188-1189.
42. Heasman MA, Kemp IW, Urquhart JD, Black R. Childhood leukemia in northern Scotland [letter]. Lancet 1986;1:266.
43. Henshaw DL, Eatough JP, Richardson RB. Radon as a causative factor in induction of myloid leukemia and other cancers. Lancet 1990:1008-1012.
44. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 1971;284:878-881.
45. Hoffmann W, Kranefeld A, Schmitz-Feuerhake I. Radium-226-contaminated drinking water: hypothesis on an exposure pathway in a population with elevated childhood leukemia. Environ Health Perspect 1993;101 Suppl 3:113-115.
46. Hoffmann W, Lotz I, Greiser E. Leukämiefälle im Landkreis Steinburg, orientierende Einschätzung der epidemiologischen Situation. Bremen Bremer Institut für Präventionsforschung und Sozialmedizin (BIPS), 1994.
47. Hole DJ, Gillis CR. Childhood leukemia in the west of Scotland [letter]. Lancet 1986;2:524-525.
48. Hostrup O, Witte I, Hoffmann W, Greiser E, Butte W, Walker G. Biozidanwendungen im Haushalt als möglicher Risikofaktor für die Gesundheit der Raumnutzer. Abschlußbericht zur erweiterten Nachuntersuchung der Fall-Kontroll-StudieMünchehagen („Nähe zu einer Sondermülldeponie und andere Risikofaktoren für die Entstehung von Leukämien, malignen Lymphomen und multiplen Myelomen"). Praxis der Biozidanwendung, cemisch-analytische Expositionserfassung uns Leukämierisiko durch Anwednung von Bioziden in Innenräumen. Bremen Bremer Institut für Präventionsforschung (BIPS), 1996.
49. Ichimaru M, Ishimaru T, Belsky JL, et al. Incidence of leukemia in atomic bomb survi-

vors, Hiroshima and Nagasaki 1950-71, by radiation dose years after exposure, age, and type of leukemia. Hiroshima Radiation Research and Effects Foundation, Technical Report RERF 10-76, 1977.

50. Infante PF, Rinsky RA, Wagoner JK, Young RJ. Leukaemia in benzene workers. Lancet 1977;2:76-78.

51. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks of chemicals to humans. Some industrial chemicals and dyestuffs. v. 29. Lyon IARC, 1982:93-148.

52. Jakobsson R, Ahlbom A, Bellander T, Lundberg I. Acute myloid leukemia among petrol station attendants. Arch Environ Health 1993;48(4):255-259.

53. Johnson CJ. Cancer incidence in an area contaminated with radionuclides near a nuclear installation. Colorado Medicine 1981;78:385-392.

54. Johnson CJ. An increase in leukemia deaths in South Dakota associated with thirty-two radioactive fallout plumes that traversed the State from nuclear bomb tests at the Nevada Test Site. International Perspectives in Public Health 1989;5:3-6.

55. Kaatsch P, Haaf HG, Michaelis J. Jahresbericht 1993 des Deutschen Kinderkrebsregisters. Mainz Institut für Medizinische Statistik und Dokumentation der Universität Mainz, 1994.

56. Kitabake TT, Watanabe T, Koga S. Radiation cancer in japanese radiological workers. Strahlentherapie 1973;146:599-606.

57. Kneale GW. Geographic and sociodemographic factors in the etiology of juvenile neoplasms: Implications for leukemia clusters of several factors including density, background radiation, infections and immunisations. In: Lengfelder E, Wendhausen H, editors. Neue Bewertung des Strahlenrisikos. Niedrigdosis-Strahlung und Gesundheit. München: MMV Medizin Verlag, 1992:141-57.

58. Leiss JK, Savitz DA. Home pesticide use and childhood cancer: A case-control study. Am J Public Health 1995;85:249-252.

59. Lyman GH, Lyman CG, Johnson W. Association of leukemia with radium groundwater contamination. JAMA 1985;254:621-626.

60. Lyon JL, Klauber MR, Gardner JW, Udall KS. Childhood leukemia associated with fallout from nuclear testing. N Engl J Med 1979;300:397-402.

61. MacMahon B. Prenatal X-ray exposure and childhood cancer. JNCI 1962;28:1173-1191.

62. MacMahon B. Leukemia clusters around nuclear facilities in Britain. Cancer Causes Control 1992;3:283-288.

63. Michaelis J, Keller B, Haaf G, Kaatsch P. Incidence of childhood malignancies in the vicinity of West German nuclear power plants. Cancer Causes Control 1992;3:255-263.

64. Monson RR, MacMahon B. Prenatal X-ray exposure and cancer in children. In: Boice JD, Fraumeni JF, editors. Radiation Carcinogenesis: Epidemiology and biological significance. New York: Raven Press, 1984:97-105.

65. Morris M, Knorr RS. Southeastern Massachusetts Health Study 1978-1986. Boston, Mass. Division of Environmental Health assessment, Massachusetts Dept. of Public Health, 1990.

66. Natarajan N, Bross IDJ. Preconception radiation and leukemia. J Med 1973;4:276-281.

67. Neutra RR. Counterpoint from a cluster buster. Am J Epidemiol 1990;132(1):1-8.

68. Pearce NE, Sheppard RA, Howard JK, Fraser J, Lilley BM. Leukemia among New Zealand agricultural workers. A cancer registry-based study. Am J Epidemiol 1986;124:402-409.

69. Prindull G, Demuth M, Wehinger H. Cancer morbidity rates of children from the vicinity of the nuclear power plant of Wurgassen (FRG). Acta Haematol 1993;90:90-93.

70. Roman E, Beral V, Carpenter L, et al. Childhood leukemia in the West Berkshire and Basingstoke and North Hampshire District Health Authorities in relation to nuclear establishments in the vicinity. BMJ 1987;294:597-602.

71. Rose G. [Preface]. In: Elliott P, Cuzick J, English D, Stern R, editors. Geographical and Environmental Epidemiology. Oxford, New York, Tokyo: Oxford University Press, 1992:VII.

72. Rothman KJ. Clustering of disease. Am J Public Health 1987;77:13-15.

73. Rothman KJ. A sobering start for the cluster busters' conference. Am J Epidemiol 1990;132(1):S6-S13.

74. Savitz DA. Epidemiologic studies of electric and magnetic fields and cancer: Strategies for extending knowledge. Environ Health Perspect 1993;101(Suppl 4):83-91.

75. Savitz DA, Ahlbom A. Epidemiologic evidence on cancer in relation to residential and occupational exposures. In: Carpenter DO, Ayrapetyan S, editors. Biological effects of electric and magnetic fields. Beneficial and harmful effects. v. 2. San Diego, New York, Boston, London, Sydney, Tokyo, Toronto: Academic Press, 1994:233-62.

76. Savitz DA, Wachtel H, Barnes FA, Johnson EM, Tvrdik JG. Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. Am J Epidemiol 1988;128:21-38.

77. Schmitz-Feuerhake I, Schroeder H, Dannheim B, et al. Leukaemia near water nuclear reactor [letter]. Lancet 1993;342:1484.

78. Shands KN, Schmid GP, Dan BB, et al. Toxic-shock syndrome in menstruating women. N Engl J Med 1980;303:1436-1442.

79. Shimizu Y, Kato H, Schull WJ. Studies of the mortality of A-bomb survivors. Mortality 1950-1985: Part 2. Cancer mortality based on the recently revised doses (DS86). Radiat Res 1990;121(2):120-141.

80. Shiono PH, Chung CS, Myrianthopoulos NC. Preconception radiation, intrauterine diagnostic radiation, and childhood neoplasia. JNCI 1980;65(4):681-686.

81. Shleien B, Ruttenber AJ, Sage M. Epidemiologic studies of cancer in populations near nuclear facilities. Health Phys 1991;61:699-713.

82. Stewart AM, Gilman EA, Kneale GW. Radiation dose effects in relation to obstetric X-ray and childhood cancer. Lancet 1970;2:1185-1188.

83. Stewart AM, Kneale GW. Age-distribution of cancers caused by obstetric X-rays and their relevance to cancer latent periods. Lancet 1970;1:4-8.

84. Urquhart J, Cutler J, Burke M. Leukemia and lymphatic cancer in young people near nuclear installations [letter]. Lancet 1986:384.

85. Urquhart J, Palmer M, Cutler J. Cancer in Cumbria: The Windscale connection. Lancet 1984:217-218.

86. Viel Jean-F, Pobel D, Carré A. Incidence of leukemia in young people around the La Hague nuclear waste reprocessing plant: A sensitivity analysis. Statistics in Medicine 1995;14:2459-2472.

87. Viel JF, Richardson ST. Childhood leukaemia around the LaHague nuclear waste reprocessing plant. BMJ 1990;300:580-581.

88. Viel Jean-F, Richardson S, Danel P, et al. Childhood leukemia incidence in the vicinity of La Hague nuclear-waste reprocessing facility (France). Cancer Causes Control 1993;4:341-343.

89. Wakeford R, Binlas K. Childhood leukemia and nuclear installations. Journal of the Royal Statistical Society A 1989;152 (part 1):61-86.

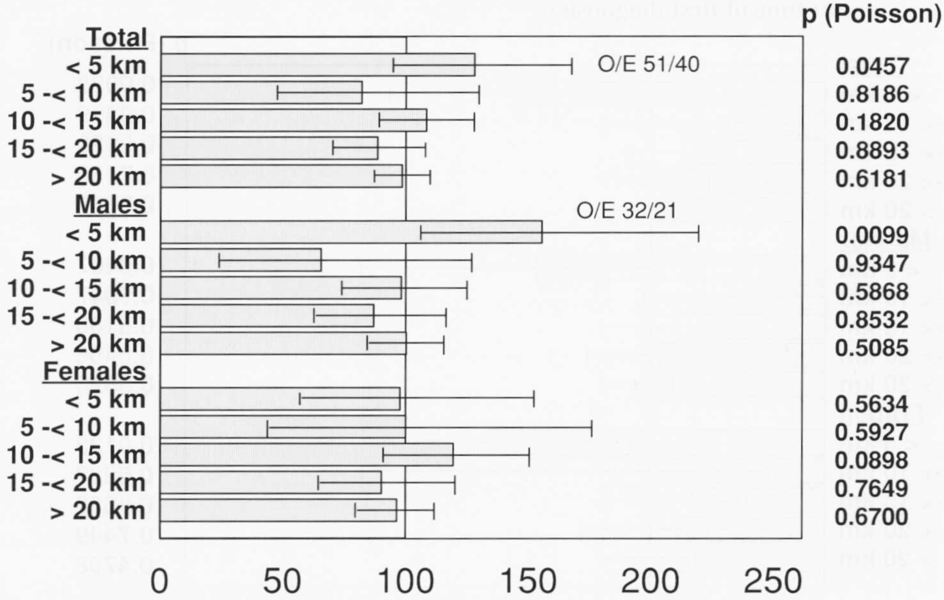
90. Washburn EP, Orza MJ, Berlin JA, et al. Residential proximity to electricity transmission and distribution equipment and risk of childhood leukemia, childhood lymphoma, and childhood nervous system tumours: Systematic review, evaluation, and meta analysis. Cancer Causes Control 1994;5:299-309.

91. Wertheimer NW, Leeper E. Electrical wiring configurations and childhood cancer. Am J Epidemiol 1979;109:237-284.

92. Wheldon TE, Mairs R, Barrett A. Germ cell injury and childhood leukemia clusters. Lancet 1989:792-793.

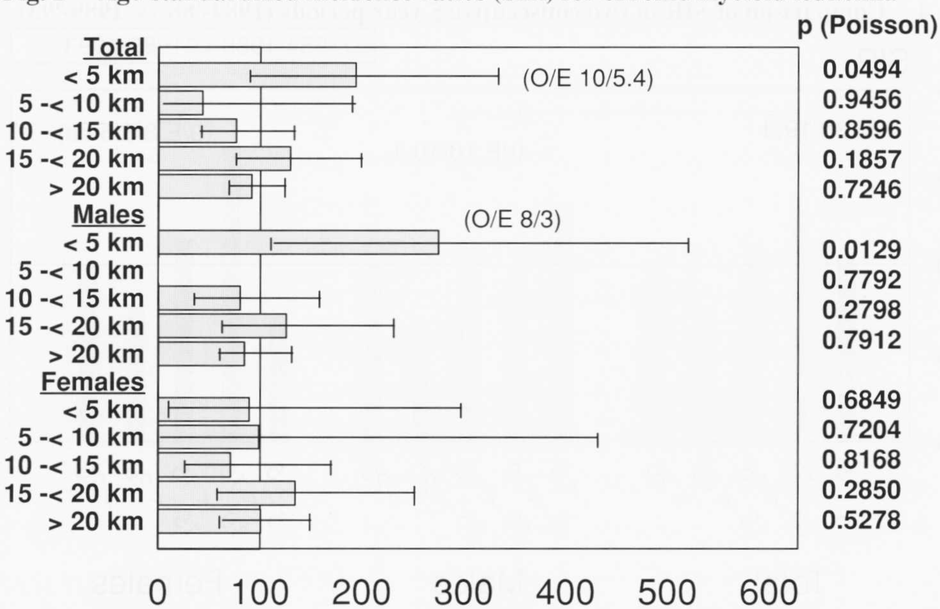
(This text is a reprint of a chapter published previously by the authors. Hoffmann W, Greiser E: Inceased Incidence of leukaemias in the vicinity of the Krümmel nuclear power plant in Northern Germany. In: Environmental Epidemiology in Europe 1995. Proceedings of an International Symposium. Frentzel-Beyme R, Ackermann-Liebrich U, Bertazzi PA, Greiser E, Hoffmann W, Olsen J (eds). Bremen Institute for Prevention Research and Social Medicine (BIPS) for the European Commission, Directorate General V, Bremen 1996, 185-206)

Fig. 1 Age-standardized incidence ratios (SIR) for all leukemias



o/e = observed/expected number of cases

Fig. 2 Age-standardized incidence ratios (SIR) for chronic myeloid leukemia



o/e = observed/expected number of cases

Fig. 3 Leukemia incidence in agegroups below 65 years (age at time of first diagnosis)

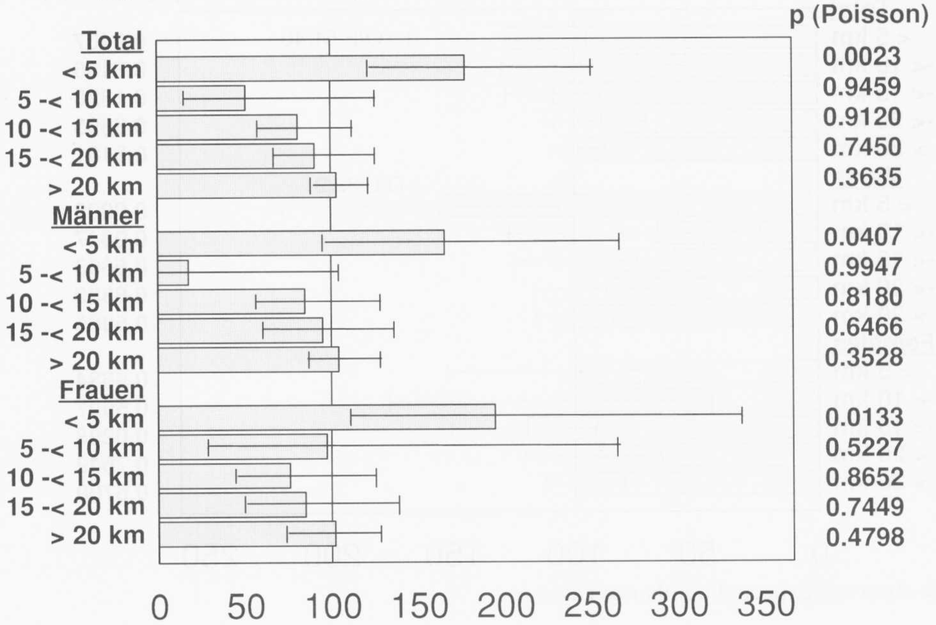
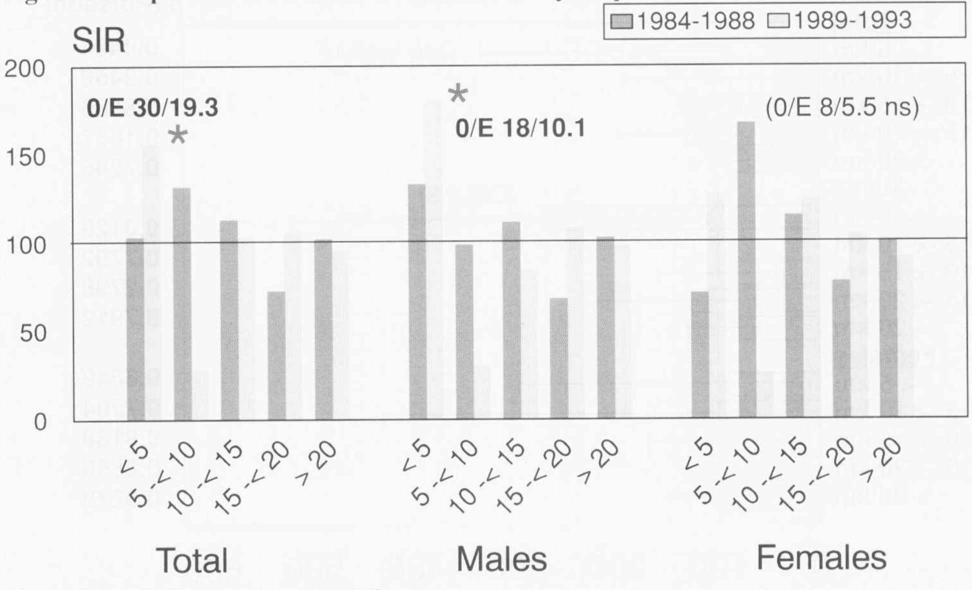


Fig. 4 Comparison of SIR in two consecutive 5 year periods (1984-'88 vs. 1989-'93)



o/e = observed/expected number of cases