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FAST TRACK

Leukaemia in young children living in the vicinity of German nuclear power plants

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A case control study was conducted where cases were children younger than 5 years (diseased between 1980 and 2003) registered at the german childhood cancer registry (GCCR). Population-based matched controls (1:3) were selected from the corresponding registrar's office. Residential proximity to the nearest nuclear power plant was determined for each subject individually (with a precision of about 25 m). The report is focused on leukaemia and mainly on cases in the inner 5-km zone around the plants. The study includes 593 leukaemia cases and 1,766 matched controls. All leukaemia combined show a statistically significant trend for 1/distance with a positive regression coefficient of 1.75 [lower 95%-confidence limit (CL): 0.65]; for acute lymphoid leukaemia 1.63 (lower 95%-CL: 0.39), for acute non-lymphocytic leukaemia 1.99 (lower 95%-CL: −0.41). This indicates a negative trend for distance. Cases live closer to nuclear power plants than the randomly selected controls. A categorical analysis shows a statistically significant odds ratio of 2.19 (lower 95%-CL: 1.51) for residential proximity within 5 km compared to residence outside this area. This result is largely attributed to cases in previous studies of the GCCR (especially in the inner zone) as there is clearly some overlap between those studies. The result was not to be expected under current radiation-epidemiological knowledge. Considering that there is no evidence of relevant accidents and that possible confounders could not be identified, the observed positive distance trend remains unexplained.

Key words: childhood; leukaemia; nuclear power plants; population-based; cancer registry

To date, the aetiology of childhood leukaemia has remained inconclusive even though numerous epidemiological studies have addressed this question. There are some risk factors discussed as possibly causal or protective include lifestyle, genetic disposition, course of pregnancy and perinatal development, the immune system and environmental hazards.[1–5] One generally accepted risk factor for leukaemia is exposure to ionising radiation.[6,7] Whether there is a threshold level at which any higher level of exposure will be associated with occurrence of leukaemias, however, is subject to controversy. Internationally, currently used estimates of cancerogenic radiation effects in the low-dose range are based on linear no-threshold extrapolation; regarding leukaemia, a quadratic model is also applicable.[8,9] Other authors work on the assumption that these models overestimate the effects in a dose range of <10 milli Sievert considerably.[10] Child-specific conclusions are either not given in these published reports or data are reported to be insufficient for any conclusions to be drawn.[8]

For many years, there has been controversy over whether or not the emission of ionising radiation during routine operation of nuclear plants will already increase the risk of leukaemia in children. Such an effect is not too likely as present-day emissions of ionising radiation from nuclear power plants in routine operation are several magnitudes lower than the value of 0.3 milli Sievert/year not to be exceeded according to the guidelines for the operation of nuclear power plants.[11,12]

In 1987 and 1989, British studies reported a statistically significant increased rate of leukaemia in under 15-year-olds within a 10-mile zone of nuclear plants in England and Wales.[13,14] These reports prompted a study of almost identical design that was based on the data of the German Childhood Cancer Registry (GCCR) and was conducted in the late 1980s. This was an ecological study comparing disease rates within 15 km (roughly 10 miles) of German nuclear plants with those seen in specified control areas. The study period extended from 1980 through 1990 (Study 1). An increased rate of all cancer or, more specifically, leukaemia in children younger than 15 years within a 15-km zone of West German nuclear plants was not confirmed. However, exploratory analyses indicated that, for example, in children younger than 5 years living within the inner 5-km zone, the increase in leukaemia rate was statistically significant.[15] As these results gave rise to controversial discussion and as at the same time a statistically significant leukaemia cluster was seen near the North German nuclear power plant of Krümmel,[16] the study period was extended to cover the years 1991 through 1995 (Study 2).

Study 2 failed to reproduce statistically significant results regarding the subgroup for which results were significantly increased in the exploratory analysis of Study 1. Nevertheless, a tendency was seen towards an increased relative risk (RR) for leukaemia to occur in under 5-year-olds within the 5-km vicinity.[17]

Even after these results had been published, discussions on a potential relationship between the occurrence of childhood leukaemia and close proximity to nuclear plants in routine operation have not ceased. For this reason, a case control study was initiated by the Federal government and started at the GCCR in 2003. In this investigation, residential proximity to the nearest nuclear power plant was determined for each subject individually. This case control study was limited to children younger than 5 years. As in Studies 1 and 2, not only leukaemia, but all childhood malignancies were included. Its scope extends well beyond the 15-km zone defined in the first 2 studies.[18] Some features regarding the design of all 3 GCCR studies are given in Table I.

The present report is focused on leukaemia and mainly on cases with place of residence in the inner 5-km zone around the nuclear power plants. Other results are published elsewhere.[19] As in most radiation-epidemiological studies, the leukaemia cases are subdivided for analysis into acute lymphoid and acute non-lymphocytic leukaemias. Considering that some leukaemia cases of the previous studies (Studies 1 and 2), and especially those from the inner zone, are identical with those included in the recent study, and data are thus not independent, this aspect will be given particular attention.

Abbreviations: CL, confidence limit; GCCR, German Childhood Cancer Registry; GPOH, German Society of Paediatric Oncology and Haematology; ICCC, International Classification of Childhood Cancer; NPP, nuclear power plants; OR, odds ratio; RR, relative risk.

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TABLE I – DESIGNS OF STUDIES ON CHILDHOOD CANCER IN THE VICINITY OF NUCLEAR POWER PLANTS (NPP) PERFORMED AT THE GERMAN CHILDHOOD CANCER REGISTRY (PREVIOUS STUDIES 1 AND 2 COMPARED TO RECENT STUDY)

Study	Study period	Study type	Study region	npp included	Age group	Cases (by disease and age)	Date published	Exposure surrogate
Study 1	1980–1990	Ecological study	15 km vicinity based on communities	18 npp and 2 research plants	<15 years	All cancers <15y: n = 812 leukaemias <15y: n = 279 leukaemias <5y: n = 153	In 1992 (15)	Community in 5/10/15 km in 1992 (15) zones
Study 2	1991–1995	Ecological study	15 km vicinity based on communities	18 npp and 2 research plants	<15 years	All cancers <15y: n = 550 leukaemias <15y: n = 182 leukaemias <5y:n = 107	In 1998 (17)	Community in 5/10/15 km zones
Recent study	1980–2003	Case control study	Counties (up to 80 km)	16 npp (subset of 18 npp)	<5 years	All cancers <5y: n = 1592 leukaemias <5y: n = 593	In 2007 (19)	Exact distance of residence from nearest npp

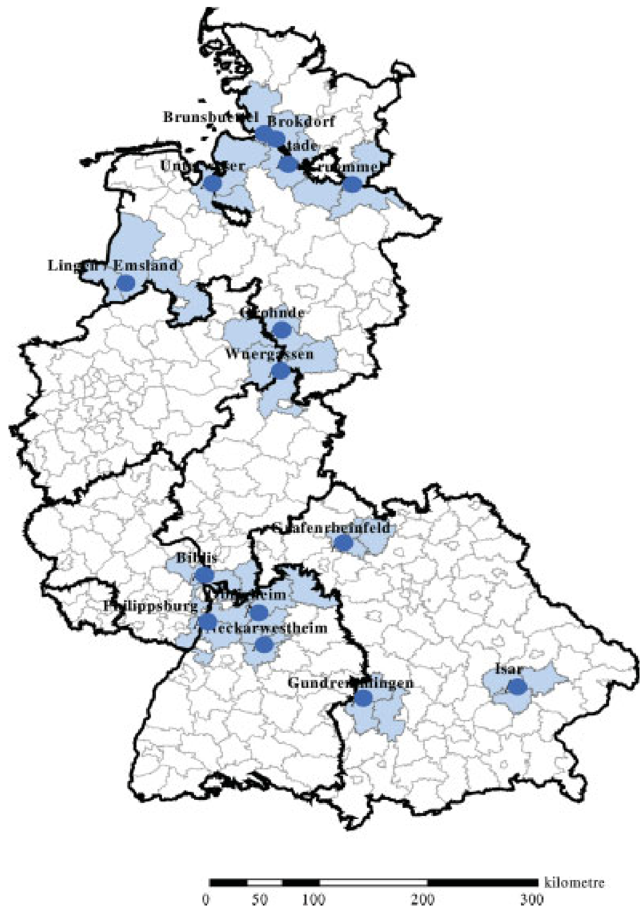

FIGURE 1 – Study region composed by different study areas (shaded counties) surrounding 16 West German nuclear power plants included (indicated by name and dots) (Lingen/Emsland to be counted twice due to a distance of 2 km between 2 different plants). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Material and methods

We conducted a case control study where cases were children registered with the GCCR for a malignant disease and population-based matched controls (1:3) were selected from the records of the corresponding registrar's office.

The geographical area covered by the study comprises 41 counties in the vicinity of 16 West German power plant sites. For each site, generally, 3 neighboring counties were identified: the county where the power plant is located, the immediately neighboring county and the next county in eastern direction (to account for prevailing westerly winds in Germany) (Fig. 1).

The study group includes all children diagnosed of a malignant disease (or nonmalignant brain tumor) from January 1, 1980 through December 31, 2003, who had been diagnosed before their fifth birthday, who were living in the study area when diagnosed, and who had been registered with the GCCR. Depending on the operation time of the plants, inclusion periods may be shorter in some areas (starting 1 year after entering operation at the earliest, ending 5 years after cease of operation at the latest). Diagnoses are classified according to the International Classification of Childhood Cancer (ICCC).[20] Leukaemia cases are grouped under ICCC category I, that is, Ia for acute lymphoid, Ib for acute non-lymphocytic leukaemia.

For all cases, controls from the records of the appropriate registrar's office were selected. The controls were matched for date of birth (as closely as possible), age, sex and nuclear power plant area (at the date of diagnosis). First, communities out of the respective area were selected randomly by weighting communities according to their population (considering sex, age, year of diagnosis). Communities were then asked to provide addresses and names of children fitting the matching criteria. From these lists, the control with date of birth closest to that of the case was selected.

The distance of the family's place of residence at the time of diagnosis (corresponding data in controls) from the chimney of the nearest nuclear power plant was ascertained. The addresses were geocoded. The main question of this investigation was whether or not the cases' places of residence are closer in proximity to the power plants than those of the random controls from the population. Analyses were performed for all leukaemia and specified diagnostic subtypes (ICCC categories Ia and Ib). A conditional logistic regression model was fitted using case control status as the independent variable. The inverse distance function was included as the continuous variable of the model. For all leukaemia combined, the possibility of a quadratic model (second order polynomial) was investigated and assessed by the Akaike information criterion. If this fits better than the untransformed modelling, the quadratic model is applied to all subtypes. For each model, the regression coefficient β was estimated and the lower one-sided 95% confidence limit (lower 95%-CL) was determined.

A secondary approach, specified beforehand, was explored by dichotomising residential proximity to the nearest power plant. The 2 categories to be compared were "residential proximity up to 5 km" and "residence at larger distance." Odds ratios (OR) and lower 95%-CL were estimated. The same procedure was applied for the 10-km distance. To compare the results of the categorical data analysis with those of the continuous variable calculation, the OR for the mean of residential proximity within the 5-km zone was derived from the estimated regression curve as well.

To ensure the correctness of our analyses, all relevant computations were repeated independently by a statistician from the coordinating centre of clinical trials of the university of Mainz.

Whereas the previous studies had determined the risk estimates as RR with two-sided 95%-confidence interval (CI), the recent study, asking a one-sided question, uses OR with lower 95%-CL. For comparison reasons, the findings of the recent study will also be reported for the time periods used in Studies 1 and 2 (1980–1990, 1991–1995 and for comparison 1996–2003), using one-sided tests.

Results

The study includes a total of 593 leukaemia cases and 1,766 matched controls. Table II shows the age and sex distribution as specified by the matching criteria and the number of cases for diagnostic subtypes.

The dose–response curve for the analysis of the continuous distance measure is shown in Figure 2. On the basis of this curve, the fitted OR at 5-km distance is 1.42 (lower 95%-CL: 1.14) and the expected mean effect inside the inner 5-km zone would be OR = 1.76 (lower 95%-CL: 1.24).

For all leukaemia combined, there is a statistically significant trend for 1/(distance in km) with a positive regression coefficient of 1.75 (lower 95%-CL: 0.65) (Table III). This indicates a negative trend for distance. Cases live closer to nuclear power plants than the randomly selected controls. The regression coefficients

TABLE II – DISTRIBUTION OF LEUKAEMIA CASES (N = 593) AND CONTROLS (N = 1766) BY SEX, AGE (YEARS) AND DIAGNOSTIC SUBTYPES

	Cases		Controls	
	Absolute	%	Absolute	%
Boys	323	54.5	963	54.5
Girls	270	45.5	803	45.5
Age 0 to 1	51	8.6	156	8.8
Age 1 to 2	102	17.2	296	16.8
Age 2 to 3	158	26.6	459	26.0
Age 3 to 4	166	28.0	498	28.2
Age 4 to 5	116	19.6	347	19.7
Age 5 to 6*	0	0.0	10	0.6
Acute lymphoid leukaemias	512	86.3	1523	86.2
Acute non-lymphocytic leukaemias	75	12.6	225	12.7
Other leukaemias	6	1.0	18	1.0

*Controls matched to cases aged 4–5.

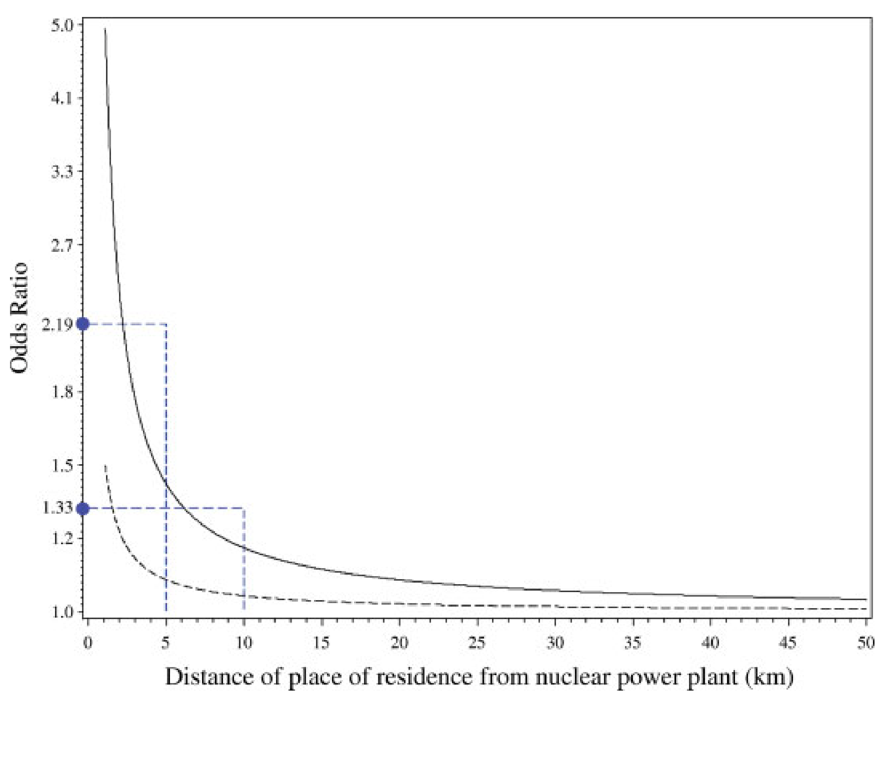

FIGURE 2 – Estimated dose response curve for leukaemias (upper curve) based on conditional logistic regression model (593 cases, 1,766 matched controls; distance axis cut off at 50 km). Lower curve: estimated lower one-sided 95% confidence band.[21] Dotted lines: categorical results for inner 5- and 10-km zone. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE III – ESTIMATED PARAMETERS FROM THE CONDITIONAL LOGISTIC REGRESSION MODEL WITH CONTINUOUS EXPOSURE (1/DISTANCE IN KM) FOR LEUKAEMIA AND SUBTYPES (UNDER 5 YEARS OF AGE)

Diagnostic group	β	Lower 95%-CL	Cases (*N*)	Controls (*N*)
All leukaemias	1.75	0.65	593	1.766
Acute lymphoid leukaemias	1.63	0.39	512	1.523
Acute non-lymphocytic leukaemias	1.99	−0.41	75	225

β, regression coefficient; 95%-CL, one-sided 95% confidence limit.

TABLE IV – ESTIMATED ODDS RATIOS (OR) AND HARMONIC MEAN OF DISTANCE FROM PLACE OF RESIDENCE TO NEAREST NUCLEAR POWER PLANT (NPP) BY DISTANCE CATEGORIES FOR ALL LEUKAEMIAS (UNDER 5 YEARS OF AGE)

Distance (km)	Harmonic mean of distance from residence to nearest npp (km)	OR derived from continuous regression model	OR categorical	Cases (*N*)	Controls (*N*)
<5	3.09	1.76	2.27	37	54
5 to <10	7.62	1.26	1.09	58	173
10 to <30	17.79	1.10	1.01	332	1048
30 to <50	37.45	1.05	1.11	135	387
50 to <70	56.98	1.03	0.90	27	92
≥70	73.59	1.02	1.00*	4	12

*Reference category.

for acute lymphoid leukaemia and acute non-lymphocytic leukaemia are 1.63 (lower 95%-CL: 0.39) and 1.99 (lower 95%-CL: −0.41); the latter value is not statistically significant because of the comparatively lower number of cases (Table III). For all leukaemias, the linear-quadratic model did not fit sufficiently better than the pure linear model.

When leaving each nuclear power plant out of the calculations one by one, the results change only marginally: the regression coefficients vary between 1.39 and 2.09, all results remain statistically significant. The maximum deviation from the overall coefficient of 1.75 is seen when analysing the data excluding the nuclear power plant of Krümmel (regression coefficient: 1.39 with lower 95%-CL of 0.14). In the surrounding area of Krümmel, a well-known increase of childhood leukaemia incidence was observed since 1990.[16]

Table IV shows the OR based on an analysis of distance categories and the OR derived from the continuous fitted curve described in Table III. The categorical model shows a relatively high OR in the inner 5-km zone, while they are near 1.00 outside this zone. The rather steeply decreasing fitted regression curve (Fig. 2) describes this observation rather well, while somewhat overestimating the effect in the 5–10-km zone.

Comparing subjects living within 5 or 10 km from the nuclear power plant with those outside the respective zone in the categorical (dichotomous) analysis, a statistically significant OR of 2.19 (lower 95%-CL: 1.51) is seen for residential proximity within 5 km compared to residence outside this area (Table V). For the 10-km zone, an OR of 1.33 (lower 95%-CL: 1.06) was observed. Regarding acute lymphoid leukaemia, the categorical analysis shows an OR of 1.98 for the 5-km zone and an OR of 1.34 for the 10-km distance (lower 95%-CLs: 1.33 and 1.05) (Table V). For acute non-lymphocytic leukaemia, the risk estimate of an OR of 3.88 (lower 95%-CL: 1.47) for the 5-km zone is almost double the risk estimate determined for acute lymphoid leukaemia and the estimate is 1.30 for the 10-km distance. However, due to the comparatively low number (10 cases) the latter is not statistically significant (lower 95%-CL: 0.66).

Table VI lists the results of the categorical analysis for 5 km and the comparable findings from the previous studies of the GCCR (Studies 1 and 2). For the total study period covered by the previous 2 studies (1980–1995), an RR of 1.49 (95%-CI: 0.98–2.20) was found. Regarding the total study period of the recent study (1980–2003), the OR is 2.19 (lower 95%-CL: 1.51). Consistency of results is predominantly seen in the first study period (1980–1990) for which the exploratory analysis of Study 1 prompted the next 2 studies: the 2 risk estimates for the first study period are nearly identical (3.01 for the previous study, 95%-CI: 1.25–10.31; 3.00 for the recent study, lower 95%-CL: 1.54). As to the time period following the previous 2 studies (1996–2003) the risk estimate of 1.78 (lower 95%-CL: 0.99) determined in the recent study is lower than that for the previous time periods.

TABLE V – ESTIMATED ODDS RATIOS (OR) FOR TWO DISTANCE CATEGORIES FOR ALL LEUKAEMIAS AND SUBTYPES (UNDER 5 YEARS OF AGE)

	OR	Lower 95%-CL	Cases in the 5-km zone (*N*)
All leukaemias			
≤5 km to >5-km zone	2.19	1.51	37
≤10 km to >10-km zone	1.33	1.06	95
Acute lymphoid leukaemias			
≤5 km to >5-km zone	1.98	1.33	30
≤10 km to >10-km zone	1.34	1.05	84
Acute nonlymphocytic leukaemias			
≤5 km to >5-km zone	3.88	1.47	7
≤10 km to >10-km zone	1.30	0.66	10

95%-CL, one-sided 95% confidence limit.

TABLE VI – RESULTS OF STUDIES ON CHILDHOOD LEUKAEMIA (UNDER 5 YEARS OF AGE) IN THE VICINITY OF NUCLEAR POWER PLANTS PERFORMED AT THE GERMAN CHILDHOOD CANCER REGISTRY (PREVIOUS STUDIES 1 AND 2 COMPARED TO RECENT STUDY)

Study periods	RR/OR	Confidence intervals/Lower confidence limits	Cases 5-km zone
Previous studies			
1980–90 Study 1	3.01[1]	1.25; 10.31[1]	*N* = 19
1991–95 Study 2	1.39[1]	0.69; 2.57[1]	*N* = 12
1980–95 Study 1 + 2	1.49[1]	0.98; 2.20[1]	*N* = 31
Recent study			
1980–1990 (period of study 1)	3.00[2]	1.54[2]	*N* = 13
1991–1995 (period of study 2)	2.10[2]	1.04[2]	*N* = 10
1980–1995 (period of previous studies 1 + 2)	2.53[2]	1.57[2]	*N* = 23
1996–2003 (period following previous studies)	1.78[2]	0.99[2]	*N* = 14
1980–2003 (total recent study period)	2.19[2]	1.51[2]	*N* = 37

Relative Risks (RR) and Odds Ratios (OR) by different study periods in the inner 5 kilometre zone (periods shown analogous to periods of previous studies).

[1]Relative risk resulting from ecological study, two-sided 95%-confidence interval. –[2]Odds ratio resulting from case control study, one-sided lower 95% confidence limit.

Discussion

Our study showed a positive relationship between the diagnosis of childhood leukaemia and the residential proximity to the nearest nuclear power plant. This result is largely attributed to cases in previous studies as there is clearly some overlap between those studies, especially regarding the findings in the inner zone around nuclear plants.

The strength of the recent study is the availability of the individual measurement of residential proximity to the nearest nuclear power plant for each subject, as opposed to the previous ecological studies based on aggregate data. The distance measurements have been established with a precision of about 25 m. Whereas the previous studies were based on a comparison of incidence rates only, we now have a case control approach.

An inverse relation to distance was used to describe the relation between proximity to the nearest nuclear power plant and the occurrence of leukaemia. A linear quadratic model did not fit better to our data. Most likely, potential exposure to radioactive emission of nuclear power plants would also be influenced by other factors such as topography or weather conditions (wind, precipitation).

Precise data on exposure would be desirable, for example, from measurement of radiation exposure in the subjects, however, such data are not available. It was therefore decided to work with the distance measure, that is, proximity to the nearest nuclear power plant. It was not possible to account for the fact that children will naturally spend time at places other than their home address. Moreover, the residential history of the study subjects was not available. However, as cases and controls may be moved before diagnosis of cancer (or before corresponding date for controls) this nondifferential misclassification would lead to an underestimation of the risk. Other potential individually sources of exposure to ionising radiation could not be obtained for the whole study group.

Overall, the willingness to supply addresses of potential control subjects was slightly lower among communities near power plants than in areas further away (control recruitment in the 5-km inner zone: 84%, outside the 5-km zone: 90%). A more restrictive general behavior of local authorities in the close neighborhood to nuclear power plants could be explained because of general concern in these regions. A sensitivity analysis excluding cases and controls from those communities who did not supply any or not all controls led to a negligible change in the parameter estimate (1.73 as opposed to 1.75). For 8.6% among a total of 2,359 study families, the distance could only be estimated using midpoint of the street or centre of the town. Most likely this has no relevant impact on the results.

The association observed may possibly be influenced by confounders (like social class, pesticides, factors influencing immunological factors, exposure to other ionizing radiation). To assess this, a subset of the study subjects (diagnosed 1993 or later) was interviewed. Because response rates vary remarkably with the distance to the plants (total response: 78% for cases, 61% for controls; response in the inner 5-km zone: 63% for cases, 45% for controls), no conclusions on the relationship between potential confounders and the reported findings can be drawn.

On the basis of the categorical analysis, our result indicates that 20 out of the total observed 37 leukaemia cases living within the 5-km zone are attributed to the fact that they are living in this 5-km zone. These are 0.8 cases/year in the under 5-year-olds or 0.3% of the roughly 6,000 German children diagnosed with leukaemia in this age group (1980–2003).

There is an abundance of publications on the issue of childhood leukaemia near nuclear plants which cannot be referenced systematically at this place (see Ref. 22 for a review). Whereas some cancer clusters in children have been found near nuclear power plants (Krümmel, Sellafield/Windscale, Dounreay),[16,23,24] it is also seen, when considering all relevant studies, that the assumption of a generally increased disease rate around nuclear power plants is not upheld.[22] A recent study has confirmed this observation for France.[25]

Generally, the radiation exposure near a nuclear power plant in routine operation is extremely small compared to exposure to ionising radiation of the general public from other sources (*e.g.*, cosmic, terrestrial or medical irradiation). While annual natural radiation exposure in Germany is about 1.4 milli Sievert and the annual average exposure from medical examinations is about 1.8 milli Sievert per year,[26] radiation exposure near German nuclear power plants is a factor of 1,000–100,000 less.[12] The reported findings were thus not to be expected under radiation biological and epidemiological considerations.

It should be noted that data of the previous GCCR studies and the recent study are not independent of each other. The increased risk estimates were thus not unexpected. The overlap of cases in the studies is given, because (*i*) those 16 nuclear power plants included in the recent study were also part of the previous studies and (*ii*) cases diagnosed between 1980 and 1995 entered both the previous studies and the recent study. The overlap especially is given for those cases reported from the inner zone while there is practically no overlap regarding cases outside the 15-km zone. The magnitude of overlap is verified by the following figures: regarding leukaemia cases lived in the inner 5-km zone, 25 out of those 37 cases of the recent study had already been included in the previous studies; only 12 cases from the recent study were thus not previously included; on the other hand, 6 cases from the previous studies are not included in the recent one.

The 11-year time period of the first of the previous studies (1980–1990) had shown a statistically significant result in exploratory subgroup analyses. This led to the following 2 studies and had a definite impact on the design of the recent study covering a total of 24 years (1980–2003). The first of the previous studies reported an RR of 3.01 for leukaemias within the 5-km zone and the recent study for the same period and group of patients an OR of 3.00 (1980–1990). Still, the results of the recent study for the 1996–2003 period, which had not been included in the 2 previous studies, also show a trend towards a risk increase.

To achieve more convincing results as from the previous ecological studies a design was chosen, in which for each subject individually the residential proximity to the nearest nuclear power plant was determined. So misclassification was reduced compared to the previous German studies, in which exposition was determined only roughly in categories of about less than 5 km, 5–10 km and 10–15 km. Additionally, new data of further 8 years are included.

The recent study confirmed previous German findings regarding leukaemia in the 5-km zone of nuclear power plants. However, regarding the period not included in the previous studies, that is, basically independent data, a tendency towards an increase of risk with closer residential proximity is also seen. In view of the fact that this result was not to be expected under current radiation-epidemiological knowledge and considering that there is no evidence of relevant accidents and that possible confounders could not be identified, the observed positive distance trend remains unexplained.

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