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Case–control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980–2003

Claudia Spix[a,*], Sven Schmiedel[a], Peter Kaatsch[a], Renate Schulze-Rath[a], Maria Blettner[b]

[a]German Childhood Cancer Registry, Institute for Medical Biostatistics, Epidemiology and Informatics, University Mainz, 55101 Mainz, Germany

[b]Institute for Medical Biostatistics, Epidemiology and Informatics, University Mainz, 55101 Mainz, Germany

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ABSTRACT

The 1984 Windscale study raised concern about a possible association between living in the vicinity of nuclear power plants and childhood cancer. No such effect for all cancers was seen in ecological studies in Germany (1980–1995). Results from exploratory analyses led to a new study.

Pre-selected areas around all 16 major nuclear power plants in Germany formed the study area. The design is a matched case–control study; cases are all cancers under five years diagnosed in 1980–2003: 1592 cases, and 4735 controls. Inverse distance of place of residence to the nearest nuclear power plant at the time of diagnosis was used as the independent variable in a conditional logistic regression model.

Results show an increased risk for childhood cancer under five years when living near nuclear power plants in Germany. The inner 5-km zone shows an increased risk (odds ratio 1.47; lower one-sided 95% confidence limit 1.16). The effect was largely restricted to leukaemia.

The results are compatible with the corresponding subgroups in the previous German ecological studies, with which this study shares most of the cases. They contrast with the lack of an effect observed or expected from other studies due to low doses from routine nuclear power plant operation.

1. Introduction

The German population has long been worried about the potential dangers and health effects of nuclear power. In 1984, the public was frightened by reports of elevated childhood cancer rates within a 10-mile zone of the Windscale (Sellafield) nuclear power plant in England, other investigations followed shortly.[1–5] The German Childhood Cancer Registry, founded in 1980, investigated whether there had been a similar increase in Germany. In an ecological study with a similar design to the UK (United Kingdom) studies,[1–4,6] the incidence rates of all cancers in children under 15 years of age during 1980–1990 in communities within a 15-km zone of all West German nuclear power plants (812 cases) were compared with those in reference communities with similar population densities and degrees of urbanisation. No statistically significant increase in risk was found (relative risk [RR] 0.97; 95% confidence interval [CI] [0.87;1.08]).[7] Nevertheless, exploratory analyses of subsets showed statistically significant results particularly for acute leukaemia in children under five years of age living in the inner 5-km zone (RR 3.01; 95%CI [1.25;10.31]). When five more years of data had been accrued

* *Corresponding author:* Tel.: +49 6131 17 3252; fax:+49 6131 17 2968.
E-mail address: kinderkrebsregister@imbei.uni-mainz.de (C. Spix).
URL: http://www.kinderkrebsregister.de (C. Spix).
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(1991–1995) the study was repeated: the RR for all cancers amongst children under 15 living within a 15-km zone was 1.05 (95% CI [0.92;1.20]) and the RR for acute leukaemia amongst children under 5 living within a 5-km zone was 1.39 (95% CI [0.69;2.57]).[8]

In the late 1990s, a third party obtained data up to 1998 from the German Childhood Cancer Registry (GCCR) by county via the Bundesamt für Strahlenschutz (Federal Office for Radiation Protection) for the State of Bavaria. The data were analysed in an exploratory manner applying linear regression to standardised incidence ratios (SIR's) by county. Elevated SIR's were observed for selected combinations of years, counties, and disease subgroups around Bavarian nuclear power plants. The GCCR criticised the methods used in this analysis.[9] Nevertheless the results, published over the Internet but never in a peer-reviewed journal and quoted briefly by the Deutsches Ärzteblatt,[10] were sufficiently alarming to the public to induce the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety to call for applications for another study. The design originated from discussions with a Bundesamt für Strahlenschutz (Federal Office for Radiation Protection)-expert committee. The design was influenced by the exploratory results of the previous studies.[11] The study is a matched case–control study in which the exposure surrogate is the distance of individual residences at the date of diagnosis from the nearest nuclear power plant. Data from 1996 to 2003 are now included.

The main question of the investigation presented here is: Is the risk of childhood cancer associated with living in the proximity of nuclear power stations? The distance measure, previously based on community midpoints, is now determined by the place of residence at the date of diagnosis. A subset of cases and controls was to be interviewed with regard to potential confounders.

Since the emissions from a nuclear power plant add only minimally to the background radiation level, no effect would be expected on the basis of the usual models for the effects of low levels of radiation, as presented by the biological effects of ionizing radiation (BEIR) – Committee and the international commission on radiological protection (ICRP).[12,13] However, these models are based mainly on data from adults, as childhood cancer is very rare. The BEIR Committee reviewed studies on leukaemia/childhood cancer of populations living around nuclear facilities but did not draw any conclusions from them, as they generally do not include individual estimates of radiation dose.[12]

This paper presents the overall results of the recent study conducted by the GCCR. Another paper presents the results for leukaemia and the comparison with the previous ecological studies in more detail.[14]

2. Materials and methods

2.1. Nuclear power plants

The study covered the data available at the GCCR for 1980–2003. The expert committee selected all 16 sufficiently large and long running German nuclear power plants, resulting in the inclusion of only West German nuclear power plants. A power plant was considered relevant for the study from 1 year after it started producing energy until 5 years after ceasing to operate (Table 1). The committee then selected areas around these power plants, with an emphasis on the east side because of the predominant west winds in Germany. For each nuclear power plant, the corresponding county, its next neighbour and usually one more county east of it were to be included. These counties define the area for this specific nuclear power plant. These areas overlap for several nuclear power plants. The total study area is shown in Fig. 1. The borders shown are county borders. As can be seen, nuclear power plants tend to sit close to district borders. A county in Germany consists either of one large city (community) or of a larger mixed/rural area with a varying number of smaller towns and villages (communities).[11]

2.2. Participants

One thousand five hundred and ninety two cases of cancer amongst children under 5 years of age, with oncologic diseases included in the International Classification of Childhood Cancer (ICCC)[15] resident in the study area at the date of diagnosis with known address and diagnosed in the relevant study period of the nearest nuclear power plant were included. All cases were matched with controls selected from the records of the appropriate registrar's offices. The controls were matched for date of birth (as closely as possible but at least within 1.5 years), age, sex and nuclear power plant area (at the date of diagnosis). Per control, a community was selected randomly out of the respective area according to the case-corresponding population (by sex, age and year of diagnosis). This community was asked to make available addresses and names of children with the matching criteria. From this address list the control closest to the date of birth of the case was selected.

Not all communities complied with our request to provide the addresses of controls. Six controls per case were requested and three of these were selected randomly. Finally, 4735 controls were used in the analysis.

For all case and control children, the geo-code of the place of residence at the date of diagnosis was obtained from the Land register.[16] For 9.9% of the case children and 8.4% of the controls, the address could not be coded and was replaced by the street mid-point (140 cases, 359 controls) or by the community or zip-code area mid-point (20 cases, 40 controls). The position of the chimney of each nuclear power plant was coded in the same way from high-resolution maps. All distances were given in metres.

2.3. Control for potential confounders

To assess potential confounding, the families of a subset of all cases and controls were invited to participate in a telephone interview covering other potential risk factors for childhood cancer.[17,18] The subset included all cases with selected diagnoses (leukaemia, lymphoma or a central nervous system tumour) diagnosed in 1993–2003 and their controls. The questions were summarised to a total of 20 potential confounders: social status, information on additional radiation exposure (parents, child), other risk factors (such as pesticides, mother's hormone intake), immune sys-

Table 1 – Relevant nuclear power plants and their operation periods and study periods

Name	Operating period	Study period
Brunsbüttel	23.06.1976 – 31.12.2003	01.01.1980 – 31.12.2003
Brokdorf	08.10.1986 – 31.12.2003	08.10.1987 – 31.12.2003
Krümmel	14.09.1983 – 31.12.2003	14.09.1984 – 31.12.2003
Stade	08.01.1972 – 31.12.2003	01.01.1980 – 31.12.2003
Unterweser	16.09.1978 – 31.12.2003	01.01.1980 – 31.12.2003
Lingen	31.01.1968 – 05.01.1977	01.01.1980 – 05.01.1982
Emsland	14.04.1988 – 31.12.2003	14.04.1989 – 31.12.2003
Grohnde	01.09.1984 – 31.12.2003	01.09.1985 – 31.12.2003
Würgassen	10.10.1971 – 26.08.1994	01.01.1980 – 26.08.1999
Grafenrheinfeld	09.12.1981 – 31.12.2003	09.12.1982 – 31.12.2003
Biblis	16.07.1974 – 31.12.2003	01.01.1980 – 31.12.2003
Obrigheim	22.09.1968 – 31.12.2003	01.01.1980 – 31.12.2003
Neckarwestheim	26.05.1976 – 31.12.2003	01.01.1980 – 31.12.2003
Philippsburg	09.03.1979 – 31.12.2003	09.03.1980 – 31.12.2003
Isar	20.11.1977 – 31.12.2003	01.01.1980 – 31.12.2003
Gundremmingen	14.08.1966 – 13.01.1977[a] 09.03.1984 – 31.12.2003	01.01.1980 – 31.12.2003

All periods right censored at 31.12.2003 (end of study) and study periods left censored at 1.1.1980 (start of childhood cancer registration). The order is roughly North to South.

a The 'gap' was intentionally included in the study period.

tem related issues (such as vaccinations, breast feeding and child's social interaction), type of region and folic acid in pregnancy. In addition, we asked about previous residences of the child.

2.4. *Statistical methods*

The main question was whether there is a monotonic descending relation between proximity of place of residence at the date of diagnosis to the nearest nuclear power plant included in the study at the time of diagnosis and the risk for childhood cancer. On the basis of the linear no-threshold low-dose effect excess relative risk-models as proposed by the BEIR Committee, the ICRP and the dispersion models presented by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), a conditional logistic regression with 1/(distance) as the continuous independent variable was used.[12,13,19] In the following 1/(distance in km) is referred to as measure of proximity. We adopted the view proposed by BEIR that a beneficial effect of radiation cannot be expected even at extremely low doses.[12] This is the basis for the one-sided analysis.

Additionally, categorical analyses were performed for the inner 5- and 10-km zones versus the respective outer zones. The results of the categorical models and the continuous model were compared by calculating the corresponding odds ratio (OR) from the continuous model, using the mean proximity of the controls in the respective inner zone. The conditional logistic regression model included one proximity measure at a time (continuous or categorical) and no other covariates.

If it is assumed that the estimated odds ratios are approximations of relative risk estimates, the categorical results can be converted to population attributable risks and to an attributable risk fraction for exposed cases with corresponding confidence intervals.[20]

The primary analysis included all cases in children under 5 years of age at diagnosis. The diagnostic groups defined in advance in the study protocol were leukaemia (ICCC Ia-e), lymphoid leukaemia (ICCC Ia), acute non-lymphocytic leukaemia (ICCC Ib), central nervous system tumours including medulloblastoma (ICCC IIIa-f) and embryonal tumours except for medulloblastoma (ICCC IVa, V and VIa). Detailed results for the leukaemia subgroups are presented elsewhere.[14] In further subgroup analyses, we divided the operating periods of the nuclear power plants by half, and we analysed only those who were to be interviewed. All regression results are presented with one-sided lower confidence limits (CL) at a significance level of 5%.

2.5. *Sensitivity analyses*

The randomness of the selection of the three matched controls from the maximum of six controls was assessed by repeating the regression using all available (up to 6) controls. The appropriateness of the fitted curve was investigated by fractional polynomial and Box–Tidwell-models for assessing the 'best fitting' curve (based on the deviance).[21,22]

Further sensitivity analyses were required in addition to those planned in advance. While 10% of the communities generally refused to provide control addresses, the proportion of refused addresses was higher (16%) amongst the communities situated in the inner 5-km zone. Therefore, the relevant analyses were repeated only for cases and controls from communities which provided control addresses.

The questionnaire part of the study raised a strong suspicion that communities might have sent the addresses of persons who were never resident in the respective community before the date of diagnosis of the corresponding case (about 5%). We therefore simulated artificial datasets by removing this 5% of controls from the analysis, assuming these 5% were either randomly distributed with respect to distance from the

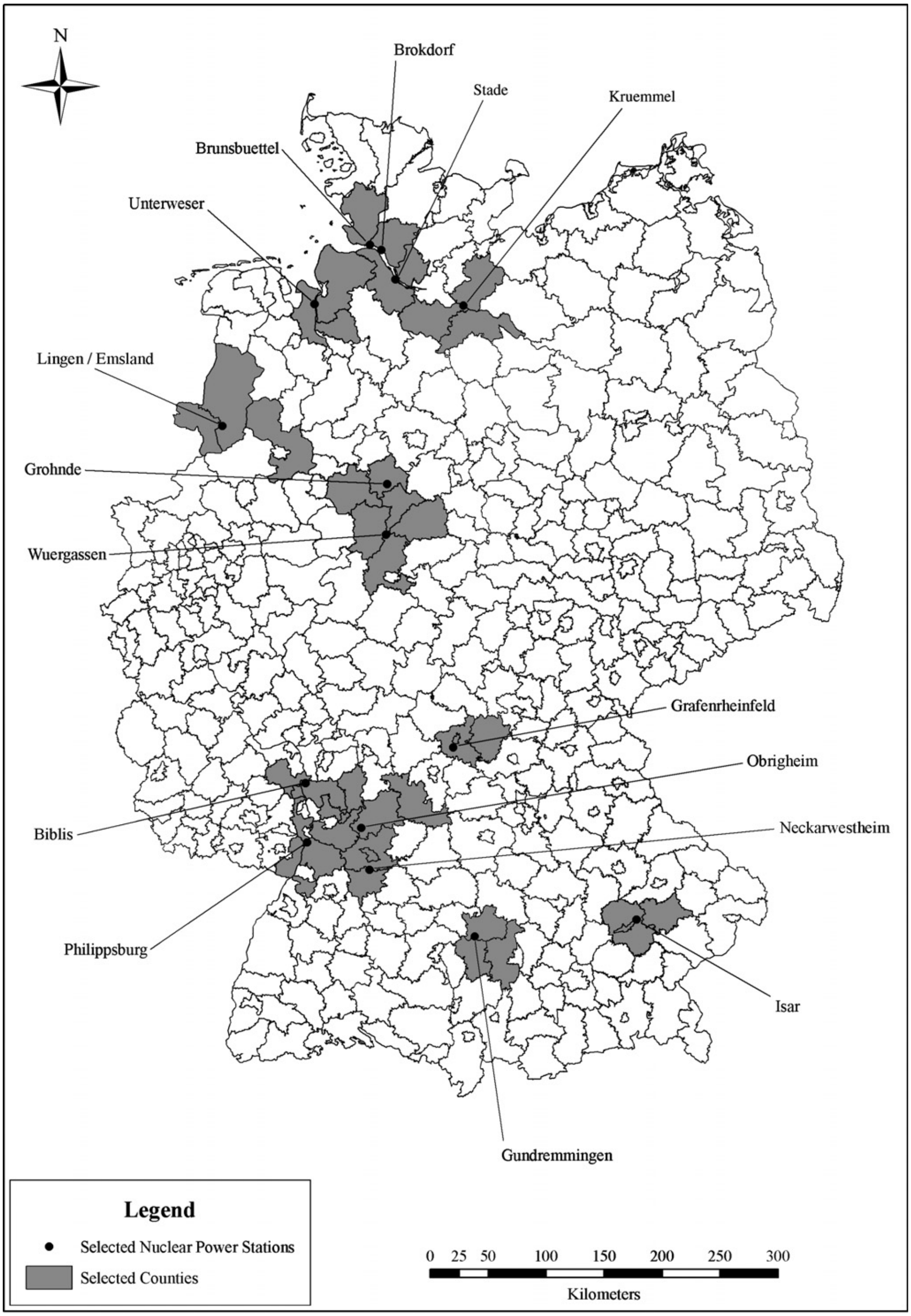

Fig. 1 – Selected nuclear power plants and study areas in Germany. Each nuclear power plant is identified by name; Lingen/ Emsland are two reactors 2 km from each other.

nuclear power plant, or more likely to live close to it or far from it. For a sub sample of the controls (45%) we were able to check the address information at the date of diagnosis of the corresponding case. Amongst these we found 15% of controls that had not lived in the indicated place at that time, though they might have lived there prior to the date of diagnosis of the corresponding case. The analysis was repeated including only controls, where the address could be checked and excluding those, whose address at the date of diagnosis of the corresponding case had been incorrect.

The previous German studies had shown single nuclear power plants to influence the results considerably, so the calculations were repeated leaving the nuclear power plants out of the analysis one by one.

As confounder assessment we planned to use a change by more than one standard deviation (out of the calculation for the respective subset of cases not including any confounder variables) of the continuous proximity parameter.

To ensure the correctness of our analyses all relevant computations were repeated independently by the coordinating centre of clinical trials (KKS) of the University of Mainz.

3. Results

Table 2 shows the characteristics of the case children and the controls. The age and sex distributions were similar, as these were matching criteria. The case children lived 1.2–81.6 km from the nearest nuclear power plant and the controls between 1.1 km and 92.0 km.

The parameter from the continuous model for the measure of proximity was $\beta = 1.18$ (lower one-sided 95% confidence limit [CL] 0.46) (Table 3, Fig. 2). The diagnostic groups defined in the study protocol showed a statistically significant effect only for leukaemia, which was stronger than the general effect (Table 2). We also give the complementary calculation beyond the study protocol (non-leukaemia cases, Table 3). No statistically significant difference was found comparing the first and second half of the respective operating periods of the nuclear power plants. The effect in the subgroup eligible for interviewing was almost the same as that in the study as a whole, although it was not statistically significant because of small numbers ($\beta = 1.05$; lower one-sided 95% CL −0.30) (Table 3).

When the continuous model was refitted with all available (maximally 6) controls per case (1592 cases, 8527 controls), the parameter estimate was $\beta = 1.18$ (lower one-sided 95% CL 0.50), which is identical to that obtained with the three selected controls (compare to Table 3). When the model was refitted after exclusion of communities that did not provide control addresses (leaving 1310 cases and 3905 controls), a statistically significant parameter estimate was found $\beta = 1.01$ (lower one-sided 95% CL 0.24) (compare to Table 3).

When 5% of all controls were either excluded randomly from the dataset with respect to their distances from the nearest nuclear power station, or selectively from close to or far from the nearest nuclear power station, we found average statistically significant estimated regression parameters of 1.18, 1.54 or 1.09, respectively, based on 1000 simulations each. These are all close to the results found with the full data (compare to Table 3). Excluding the controls from the analysis, which had their address at the date of diagnosis checked and found incorrect, led to an estimated regression parameter of

Table 2 – Characteristics of cases of all malignancies in children under 5 years of age, as defined by the ICCC,[9] diagnosed in 1980–2003 resident in the study areas, and their matched controls

	Cases		Controls	
	N	%	N	%
All	1592	100.0	4735	100.0
Boys	893	56.1	2656	56.1
Girls	699	43.9	2079	43.9
Age (years)				
0–<1	344	21.6	1016	21.5
1–<2	330	20.7	984	20.8
2–<3	340	21.4	991	20.9
3–<4	315	19.8	947	20.0
4–<5	263	16.5	775	16.4
5–<6	0	0.0	22	0.5
Diagnostic groups[a]				
Leukaemia	593	37.3	1766	37.3
Central nervous system tumours	242	15.2	720	15.2
Embryonal tumours	486	30.6	1447	30.5
Other	271	17.0	802	16.9
First half of power plant operation period	698	43.8	2073	43.8
Second half of power plant operation period	894	56.2	2662	56.2
Eligible for interview (1993–2003, selected diagnoses)	471	29.6	1402	29.6
Distance from nearest nuclear power plant (km)				
<5	77	4.8	148	3.1
5–<10	158	9.9	464	9.8
10–<20	523	32.9	1589	33.6
20–<30	403	25.3	1181	24.9
30–<40	225	14.1	726	15.3
40–<50	137	8.6	371	7.8
⩾50	69	4.3	256	5.4
Mean proximity measure[b] in the inner 5-km zone	0.3133	–	03245	–
Corresponding harmonic mean distance (km)	3.2		3.1	

a Controls matched to cases with respective diagnosis.
b Proximity measure = 1/distance in km (kilometres).

Table 3 – Estimated parameters from the conditional continuous logistic regression model for all cancers, diagnostic groups and some relevant time periods

	Estimated regression coefficient	Lower one-sided 95% confidence limit	*N* cases	*N* controls
All malignancies 1980–2003	1.18	0.46	1592	4735
Diagnostic groups 1980–2003				
Leukaemia	1.75	0.65	593	1766
Central nervous system tumours	−1.02	−3.40	242	720
Embryonal tumours	0.52	−0.84	486	1447
All malignancies except leukaemia	0.76	−0.20	999	2969
First half of power plant operation period	1.89	0.85	698	2073
Second half of power plant operation period	0.54[a]	−0.47	894	2662
Eligible for interview: diagnosed 1993–2003 with leukaemia, lymphoma, or a central nervous system tumour	1.05	−0.30	471	1402

a The difference between the first and the second half was not statistically significant.

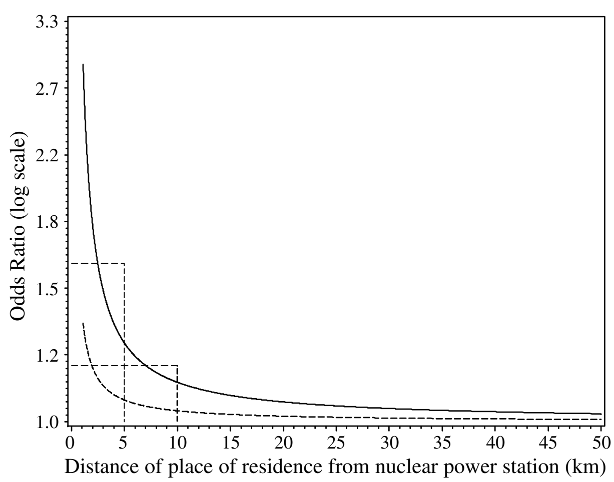

Fig. 2 – Graphical representation of the main regression analyses. Estimated regression curve for all malignancies versus distance from nearest power plant, based on 1592 cases and 4735 matched controls based on conditional logistic regression modelling. Distance axis cut off at 50 km. Black line: continuous fitted regression curve. Dotted curved line: lower one-sided 95%-confidence limit of continuous fitted regression curve. Dotted straight lines: categorical analysis for <5 km and <10 km respectively.

1.05, which again does not differ much from the full data (compare Table 3).

Leaving the nuclear power stations out of the data set one by one yielded statistically significant regression coefficients close to the overall estimate.

Fractional polynomial modelling and the Box–Tidwell model both suggested that an alternative measure of proximity of the form $1/\sqrt{(\text{distance})}$ would fit slightly better than 1/(distance), but not significantly so.

The categorical analyses showed a statistically significant effect for children living in the inner 5-km zone OR = 1.61 (lower one-sided 95% CL 1.26). Comparing diagnostic groups, the effect was again found only for leukaemia (OR = 2.19; lower one-sided 95% CL 1.51). Living in the inner 10-km zone had a far smaller effect (OR = 1.18; lower one-sided 95% CL 1.03). The fitted curve for all malignancies predicted similar OR's for the inner 5-km and 10-km zone as obtained by the categorical analysis (Table 4, Fig. 2).

Based on the categorical analysis, our result indicates that 29 out of the total observed 77 cases (38%; 95% CI [24%;61%]) diagnosed in the inner 5-km zone in 1980–2003 may be attributed to the fact that they were living in this 5-km zone. These were 1.2 cases per year, representing 0.2% (95% CI [0.1%; 0.4%]) of all 13,373 cases of cancer in children under 5 years in Germany in those years.

4. Discussion

4.1. *Principal findings*

Our results show an increased risk for cancer amongst children under 5 years of age living in the proximity of nuclear power plants in Germany. The continuous model, in agreement with the categorical analyses, identified the inner 5-km zone as the zone of increased risk (about 1.5-fold higher). The observed effect was largely restricted to leukaemia (Tables 3, 4).

Expression of the categorical estimate for living in the inner 5-km zone as an attributable risk fraction would attribute 29 out of 77 observed cases (38%; 95% CI [24%;61%]) in 1980–2003 to having lived in that zone representing 0.2% (95% CI [0.1%;0.4%]) of all 13,373 childhood cancer cases under 5 years in 1980–2003 in Germany.

4.2. *Previous studies*

The associations found in our study were strongest for leukaemia in children under 5 years of age living within a 5-km zone of a nuclear power plant. This group had yielded the most notable exploratory result in the first of the previous ecological studies.[7,8] It has to be pointed out that the cases of this study diagnosed in the study years 1980–1995 had already been included in the previous studies and that the results pre-

Table 4 – Estimated odds ratios from the conditional categorical and continuous logistic regression models for all cancers and for diagnostic groups

	OR for inner 5 km derived from continuous model[a]		Modelling 5-km distance categorically		OR for inner 10 km derived from continuous model[b]		Modelling 10-km distance categorically	
	OR	Lower one-sided 95% confidence limit	OR	Lower one-sided 95% confidence limit	OR	Lower one-sided 95% confidence limit	OR	Lower one-sided 95% confidence limit
All malignancies	1.47	1.16	1.61	1.26	1.23	1.09	1.18	1.03
Diagnostic groups								
Leukaemia	1.76	1.24	2.19	1.51	1.37	1.12	1.33	1.06
Central nervous system tumours	0.72	0.33	0.81	0.37	0.83	0.54	1.03	0.71
Embryonal tumours	1.19	0.76	1.20	0.75	1.10	0.86	1.05	0.81

Cases diagnosed/controls resident in the study area in 1980–2003.
OR: odds ratio.
a Using the mean proximity measure of the controls in the inner 5-km zone: 1/(distance in km) = 0.3245.
b Using the mean proximity measure of the controls in the inner 10-km zone: 1/(distance in km) = 0.1786.

Table 5 – Results of studies on all malignancies under the age of 5 years in the vicinity of nuclear power plants performed at the German Childhood Cancer Registry: previous studies 1 and 2 compared to recent study (categorical estimates)

Study periods	Relative risk estimate/Odds ratio	95%-confidence interval/lower one sided 95% confidence limit	Cases 5-km zone
Previous studies			
1980–1990 Study 1	1.43	[0.89; 2.43][a]	45
1991–1995 Study 2	0.97	[0.50; 1.89][a]	22
1980–1995 Study 1+2	1.24	[0.84; 1.85][a]	67
Recent study: Results shown for previous studies' study periods, for the period following the previous studies and for the total study period			
1980–1990 (period of study 1)	1.99	1.33[b]	31
1991–1995 (period of study 2)	1.41	0.90[b]	20
1980–1995 (period of previous studies 1 + 2)	1.70	1.26[b]	51
1996–2003 (period following previous studies)	1.45	0.96[b]	26
1980–2003 (total recent study period)	1.61	1.26[b]	77

Relative risks and odds ratios by different study periods in the inner 5-km zone (periods shown analogous to periods of former studies).
a Relative risk resulting from ecological study, two-sided 95% confidence interval.
b Odds ratio resulting from case–control study, lower one-sided 95% confidence limit.

sented here are consequently not entirely independent. Table 5 summarises the findings from the previous studies for all malignancies, cases under the age of five in the inner 5-km zone. It compares them with the results of this case–control study split up by the previous study periods (1980–1990, 1991–1995) and separating the new study years (1996–2003). The observed effect estimate is larger in the earliest study period (Table 5). This corresponds to the observation, that the regression parameter is larger in the first half of the nuclear power plant operation periods, though not significantly so (Table 3). While the ecological effect estimates are smaller, they are generally in the same order of magnitude (Table 4). It is thus unlikely, that the previous findings were affected by ecological bias in a major way.

This issue will be discussed more thoroughly for leukaemia in a separate paper.[14]

4.3. *Strengths and weaknesses*

The GCCR, founded in 1980, is a nationwide childhood cancer registry cooperating with all paediatric oncology units and therapy optimisation studies in Germany. Registration for cases under the age of 15 is 95% complete since the mid-1980ies.[23] Almost all cases are registered with their full address at the date of diagnosis. Given this data base, this is one of the largest studies with this objective world wide (1592 cases, including 593 leukaemia cases).

Distance to the nearest nuclear power plant at the date of diagnosis is a crude surrogate for potential exposure to radiation, however, it does not account for topography, weather, vegetation, differences in background radiation, other sources of individual exposure to radiation or the time actually spent by the individual in the home. Information on previous residences of the child from the questionnaire could not be used in the analysis due to poor and selective participation in the questionnaire part of the study (see below). The extremely low number of parents reporting occupation in a nuclear installation (0 cases, 4 controls) did not allow evaluating an effect of parental radiation exposure.

The former studies investigated only the inner 15-km zone. In the case control study, the study areas around the nuclear power plants were very large and included cases and controls from up to about 100-km distance from the nuclear power plants, which increases the statistical power slightly. Adding unexposed cases and controls does not, however, cause bias.

German nuclear energy providers are required to maintain the exposure of the population below 0.3 mSv/year.[24] Compared to this, the annual background radiation exposure estimated for the German population is 1.4 mSv/year. The average annual dose of persons of any age from medical procedures is 1.8 mSv, though this is lower for children (no specific figures given).[25] The actual emissions from nuclear power plants are far lower; e.g. for a 50-year-old person in 1991 living 5 km from one of the German nuclear power stations included in the study, the expected cumulative exposure to atmospheric discharges would have ranged from 0.0000019 mSv (Obrigheim) to 0.0003200 mSv (Gundremmingen).[26] At these levels of radiation, no detectable effects are expected from the usual models.[12,13]

The sensitivity analyses for the various expected and unexpected problems in control recruitment yielded statistically significant regression parameters of a similar magnitude to that reported in Table 2. We conclude that the biases due to these problems were small and the results cannot be explained by the biased control recruitment. The specificity of the effect for leukaemia makes it unlikely that biased control recruitment is the explanation for the effects seen in this study. The analysis excluding the nuclear power station areas one by one showed that the result is not caused by a specific nuclear power plant.

With regard to uncontrolled confounding, there may be other risk factors close to nuclear power stations, although no risk factors of the necessary strength for this effect are known for childhood cancer and specifically childhood leukaemia. We saw considerable self-selection by the persons who were to be interviewed, so that those who were interviewed were not representative of the study population as a whole, particularly with respect to their distance distribution from nuclear power plants. Assessing the change in the (biased) estimate by confounders as planned nevertheless, showed that none of them changed the distance parameter estimate by more than one standard deviation. This is true for all diagnoses investigated in the survey subset of the study as well as for diagnosis subgroups.

4.4. *International context*

The best-known quantitative summaries of current knowledge on the effects of environmental low-dose radiation effects are based mostly on adult data. Children are included, but their small number makes a negligible impact. These models deal mainly with solid tumours and adult leukaemia, applying them to children or to acute leukaemia should be done with caution.[12,13] The BEIR Committee has refused to assess studies of residents living near nuclear facilities, many of which had childhood cancer as the main objective, because of lack of actual data on exposure. They are reviewed, but not summarised or discussed beyond this.[12] Many other studies have addressed the health risks of children of parents exposed (occupationally or to radiation from the atomic bombs dropped in Hiroshima and Nagasaki) and these are therefore not comparable. If we had nevertheless applied the models proposed for adults, no detectable effect would have been predicted.

A French study of a design similar to that of the earlier incidence studies in Germany, in which SIR were computed for communities by distance, found no elevated SIR for leukaemia amongst children under five living in the inner 5-km zone of French nuclear installations (670 cases, SIR 0.97; 95% CI [0.69;1.33]).[27] When this study was repeated, with distance replaced by estimated gaseous discharges, neither the highest exposure category ($\geqslant$0.001 mSv/year; 750 cases, SIR 0.93; 95% CI [0.30;2.17]), nor any other exposure category was associated with an elevated SIR for leukaemia.[28] A recent study addressed the risk for leukaemia of children under six years of age in countries near the Chernobyl site (421 cases), on the basis of estimated cumulative doses from gaseous discharges and from food, derived from individual residence histories. This study estimated an OR of 1.46 (95% CI [1.00;2.12]) for doses between 1 and 5 mGy compared with <1 mGy.[29] 1 mGy is a far higher exposure than from a nuclear power plant under regular conditions in Germany.[26]

For some of the nuclear power plants in relatively isolated communities in northern Britain, Kinlen suggested population mixing as a potential cause of elevated leukaemia risks.[30] We inspected migration figures,[31] but there are no indications that any of the nuclear sites investigated here were particularly isolated and all have average migration at any time during the study period. This is not to say that infective causes may not in principle be an alternative explanation for the patterns we see in this study.

5. Conclusion

The design of this study aimed to clarify issues raised by previous ecological studies in Germany by using the same data plus more recent cases in a case–control study assigning individual distance estimates (as compared to community based zones). In Germany 1980–2003 we see an increased risk for cancer in children under 5 years of age, particularly leukaemia, when living in proximity (<5 km) to a nuclear power station. This observation is not consistent with most international studies, unexpected given the observed levels of radiation, and remains unexplained. We cannot exclude the possibility that this effect is the result of uncontrolled confounding or pure chance.

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Conflict of interest statement

All authors declare that they have no conflict of interest and no organisational, personal or financial connection with other people or organisations that could inappropriately influence this work.

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