**Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants (KiKK-Study)**


## Summary

### Background

The German Childhood Cancer Registry (Deutsches Kinderkrebsregister, DKKR) carried out an epidemiological case-control study which started in 2003 and was intended to find out whether cancer in children under 5 years of age is more frequent in the immediate vicinity of nuclear power plants (NPP) than further away. This study was motivated by a series of exploratory evaluations of former studies conducted by the DKKR using a different method estimating the cancer incidence of children near German NPPs. This was followed by exploratory analyses of data from the DKKR carried out by third parties based on data sets used and published by the Federal Office for Radiation Protection (BfS) for their studies, mainly for the purpose of environmental health reports. The present study consists of two parts: Part 1 is a case-control study without case or control contact, whereas for Part 2 interviews were carried out in a subgroup of cases and controls from Part 1. The study design was defined in consultation with an Expert Committee assembled by the BfS. The hypothesis of the study (in terms of the statistical null hypothesis) is: "There is no relation between the vicinity of a residence to a NPP and the risk of cancer up to the $5^{th}$ year of life. There is no negative trend of the disease risk with distance".

### Material and Methods

A case-control study was carried out. Part 1 includes all cases of children reported to the German Childhood Cancer Registry, diagnosed with cancer between 1980 and 2003, who were under 5 years of age at the time and living in preassigned regions around 16 German nuclear power plants (1,592 cases). Controls of equal sex and age in the year of the diagnosis of the disease were chosen randomly for each case (4,735 controls). The individual distance of the residence was determined on the day of diagnosis for the cases, and on a corresponding reference date for the controls.

For Part 2 of the study, a subgroup of cases and controls from Part 1 was questioned about potential risk factors which might act as confounders and about their residence history. For this purpose, the cases diagnosed between 1993 and 2003 who were less than 5 years of age, affected by leukaemia, lymphoma or a CNS tumour, and living in the study region at the time of the diagnosis were selected. The controls assigned to theses cases in Study Part 1 were also used in Part 2.

### Results

#### *Data*

The appropriation of the addresses of cases and controls and their geological coding could largely be carried out as scheduled. There was only very little missing or inaccurate information. The predefined accuracy of at least 100 m for the distance

to be determined between dwellings and the nearest NPP was fulfilled to an estimated average accuracy of approximately 25 m.

Control recruitment showed that communities in the vicinity of NPPs were less cooperative in providing control addresses (84 per cent control addresses provided, compared to 90 per cent elsewhere) than those further away.

78 per cent of the cases and 61 per cent of the controls were willing to participate in the survey in Part 2. The case-control relationship of 1:2 which had been targeted was achieved.

For a random sample of participants the information given was validated by comparing it with copies of medical records (maternity card, check-up pass, vaccination pass). The statements concerning vaccinations and data relevant to childbirth (body weight and height at birth, week of pregnancy at birth) proved to be consistent with the records.

A comparison of survey participants and non-participants revealed that participation of families was less frequent when the specific day in question (time of diagnosis for case children, corresponding reference day for control children) was longer ago (1993-1995, i.e. about 10 years before the interview). The most obvious influence on the willingness to participate proved to be the distance from the nearest NPP: within the inner 5-km area the willingness to participate was considerably lower, and this was even more pronounced in controls (46 per cent within the area compared to 62 per cent outside of it) than in cases (63 per cent compared to 79 per cent outside). We conclude that families living in the immediate vicinity of a NPP are very well aware of this fact and, therefore, tend to be more reticent when questioned.

A short questionnaire was sent to all potential participants in the survey of Part 2. Families of higher social status appeared to be more willing to participate, especially in controls. This phenomenon is known from other epidemiological and empirical studies (in Germany and internationally).

### *Confirmatory analysis*

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The main hypothesis for Part 1, i.e. that no monotonic decreasing relation exists between the distance of the dwelling from the next NPP and the risk of disease, was rejected at the one-sided level $\alpha$ = 5 per cent. 1/r was predefined as a distance measure, whereby r is the distance between the home address and the nearest NPP. Regression analysis resulted in an estimate for the regression coefficient of $\hat{\beta}$ = 1.18 (lower one-sided 95-per-cent confidence limit = 0.46, i.e. statistically significant different from zero). Evaluation of the secondary question, for which the distance is considered as a categorical variable, also shows a statistically significant result (estimated Odds Ratio (OR) = 1.61, lower one-sided 95-per-cent limit =1.26) for the 5-km area around the NPPs.

In the diagnostic subgroups, leukaemia (593 cases, 1,766 controls) showed a statistically significant estimate of the regression coefficient of $\hat{\beta}$ =1.75 (lower one-sided 95-per-cent confidence limit = 0.65). The effect observed in the subgroup of all leukaemias is stronger than that of all malignancies. The leukaemia subgroups in

the study each exhibited similar values. However, this is only statistically significant in the case of acute lymphatic leukaemia. The number of cases of acute myeloid leukaemia was too small (75 cases, 225 controls). In the other predefined diagnostic subgroups (CNS-tumours, embryonal tumours) there was no evidence of distance dependency. It may be concluded that the effect observed in all malignancies is mainly due to the results of the relatively large subgroup of leukaemias.

There is no statistically significant difference between the regression coefficients in the predefined subperiods (first half of the prevailing reactor life span compared to the second half) (p=0.1265).

The members of the subgroup of cases and controls contacted in Part 2 of the study (471 cases, 1,402 controls) show no relevant difference with respect to the regression parameter determined for the whole group in Part 1 (estimated coefficient 11 per cent less than overall model). However, the group of people participating in the interview differs considerably from the complete group.

A statistical criterion was defined in the analysis plan to determine whether the participants in the telephone interview (Part 2) were possibly a non-representative selection of the cases with corresponding diagnoses from Part 1 and the controls related to them. In which case the results of Part 2 could not be used to interpret the results of Part 1. This criterion was fulfilled, i.e. the data from the interviews in Part 2 of the study cannot be used to check whether the results of Part 1 have been biased by potential confounders. The reason is mainly based on reluctance to participate within the inner 5-km-area.

***Sensitivity analyses and explorative analyses***

A series of sensitivity analyses and exploratory analyses was carried out, some of which were planned whereas others resulted from the data situation. On the whole there was no evidence of any relevant influence on the results. Most of the sensitivity analyses tend to show a slight overestimation of the effect reported.

The planned exploratory analyses of the shape of the regression curve using fractional polynomials and a Box-Tidwell-Model showed no evidence of a basic difference of the shape of the regression curve to that intended in the analysis plan.

Since the provision of control addresses by the communities in the vicinity of NPPs was less exhaustive than by the more remote communities, a sensitivity analysis was carried out in addition to the specifications of the analysis plan. The potential bias due to this problem of control recruitment is minimal.

Interviews on residence history (Part 2) revealed that some of the control families had only lived at the originally registered addresses after the day of reference and at no time before it. This is because incorrect control addresses had been provided by the registration offices. Simulations, an extended evaluation of control recruitment data, and verification in a random sample of community registration offices showed that this was of only marginal influence on the result of the study.

Omitting one NPP region at a time (for all malignancies and leukaemias, respectively) showed no indication that the result depends solely on one individual region. It should

be noted, with regard to the heated discussion in Germany on the increased incidence of leukaemia in children living near the NPP Krümmel (as a result of 17 cases of leukaemia between 1990 and 2006 in two neighbouring communities), that 8 of these cases are within the inner 5-km study area. As regards leukaemia, the NPP Krümmel has the biggest influence on the result of the study. If these cases and the corresponding controls are omitted, the estimate for the regression coefficient in the subgroup of leukaemias is $\hat{\beta} \Xi 1.39$ (lower one-sided 95 per-cent confidence limit=0.14).

### *Confounder Analyses*

The results of Part 2 cannot be used to interpret the results of Part 1, because a selection occurred, as willingness to participate depended on the distance between the home and the NPP. Nevertheless, a multivariate regression analysis was carried out on the request of the BfS and the Expert Commission using the data collected (confounder analysis). The question of whether allowance for potential confounders would change the estimated regression coefficient of the distance measure was looked into (change-in-estimate principle), as originally intended. Thishad been the motivation for conducting Part 2 of the study. None of the variables led to changes in the estimate which exceeded the preset range ( ±1 standard deviation).

An exploratory evaluation of the confounders which this study, however, was not designed for, revealed correlations which largely confirmed the results known from literature.

### *Attributable Risks*

The risk attributable to living within a 5-km area of one of the 16 nuclear power plants in Germany between 1980-2003, and for the number of cases observed in the 5-km area under study (n=77) is 0.2 per cent. This means that under the model assumptions, 29 of the 13,373 cases diagnosed with cancer at less than 5 years of age from 1980 to 2003 in Germany, i.e. 1.2 cases per year, could be attributed to living within the 5-km area of a German NPP. In relation to the cases of leukaemia, of which 37 were observed at up to 5 years of age between 1980 and 2003 within the inner 5-km area, a 0.3 per-cent population attributable risk was calculated, i.e. 20 of 5,893 cases under 5 years of age in Germany which were diagnosed between 1980 and 2003, making 0.8 cases per year. These estimates are rather inconclusive because they are based on a very small number of cases.

## Discussion

### *Study design*

This Study is a case control study on children of less than 5 years of age who were diagnosed with cancer between 1980 and 2003. The study investigated the question of whether there is a relationship between the distance from the residence to the nearest NPP and the risk of developing cancer. The strength of this study is its application of an individual distance measure, based on the distance between homes and the nearest NPP. It thus complements the NPP studies which have been

conducted in Germany up to now based on aggregated incidence rates in vicinity regions.

The interviews of a preselected subgroup of parents of case and control children integrated into the study were intended to take potential confounders into consideration in order to use this information for the evaluation of the study result. This analysis was unfortunately not possible, or rather could not be evaluated because of the paticipants' response behaviour. There are, however, hardly any risk factors known in present literature which could act as sufficiently strong confounders.

***Radiation epidemiological aspects***

The present study considers the distance from the nearest NPP. Data on radiation exposures due to environmental conditions were not used because they are not available, nor can they be collected retrospectively. Neither was it taken into consideration that individuals do not stay in the same place constantly and that beyond the natural radiation background they are also exposed to other sources of radiation (e.g. terrestrial radiation, medical diagnostics, air travel). Varying topographic or meteorological conditions (e.g. precipitation, wind direction) could not be allowed for either.

The distance applied was that of each individual's home from the nearest NPP at the time of diagnosis (control: date of diagnosis of matched case). Taking into account home moves during the time from conception to diagnosis would have necessitated the interviewing of the families under study and was, therefore, not possible for most of the families involved.

A distance measure based on a predefined model was decided on and a regression curve was estimated for it. The distance measure was based on theoretical dispersion models, and the regression model corresponds to the standard linear model for the low-dose range. This model however is based on studies evaluating the cancer risk in adults in relation to ionising radiation. Adults predominantly develop solid tumours, whereas systemic diseases are relatively more frequent in children. It has not so far been clarified in international literature as to what extent models describing low-dose radiation effects can be transferred to leukaemia incidence in children of pre-school age.

The estimates of low-dose radiation effects presently used on the international level are based on the assumption of a linear no-threshold extrapolation, an additional option for leukaemia is a quadratic model. Other authors suggest that these models considerably overestimate the effects in the dose range < 0.01 Sv (Sievert). Special statements about children are not made in the relevant reports, or the data is described as insufficient for this purpose. The models for example specify an excess relative risk, which could be compared with the dimension OR-1 in the current report, of 0.5 per Gy per year (one Gray (Gy) corresponds to 1 Sievert). The limit of exposure for persons in the "proximity" of nuclear technical plants in Germany is 0.3 mSv (milliSievert) per year. The effective exposure is much lower. For example, a 50-year-old living at a distance of 5 km from a NPP is expected to accumulate from 0.0000019 mSv (milli Sievert)(Obrigheim) to 0.0003200 mSv(Grundremmingen) through exposure to airborne emissions from Obrigheim and Grundremmingen,

respectively. Annual exposure in Germany to the natural radiation background is approximately 1.4 mSv and the annual average exposure through medical examinations is approximately 1.8 mSv. Compared to these values, the exposure to ionising radiation in the vicinity of German NPPs is lower by a factor of 1,000 to 100,000. In the light of these facts, and based on the present status of scientific knowledge, the result of our study cannot be explained radiobiologically.

### *Comparison with previous German NPP-studies*

Before the present study was carried out, the German Childhood Cancer Registry had conducted two studies involving incidence comparisons in connection with NPPs. The first study ("Study 1") considered the incidence of all the cancer cases diagnosed from 1980 to 1990 of individuals under 15, living within 15 kilometres of any of 20 German NPPs as compared to demographically similar comparison regions. The study was motivated by the conspicuous findings within a range of 10 miles of British NPPs (Sellafield, Windscale) and the main issue was to examine all children diagnosed at 0-14 years of age within a 15-km area. No increased risk was found (RR 0.97; 95-per-cent CI [0.87;1.08]). Age subgroups, vicinity regions, and diagnosis subgroups were examined by way of exploratory analysis.

The exploratory additional results were verified in a subsequent study ("Study 2") based on the same design and using independent, updated data from 1991-1995. The central question (all diagnoses, age 0-14, 15-km area) remained the same, the corresponding result was unremarkable (RR 1.05; 95 per cent CI [0.92; 1.20]). The significant exploratory results from the first study , especially those pertaining to the question of leukaemia in children of less than 5 years of age living within the 5-km area, then revealed slightly lower relative risks and were statistically insignificant. Consequently, this was regarded as non-confirmation of the exploratory results.

The previous studies and the present study overlap with respect to the cases and the regions examined, especially in the vicinity of the NPPs. In contrast to the previous studies the BfS Expert Committee excluded the nuclear plants Kahl, Jülich, Hamm, Mühlheim-Kärlich, and Karlsruhe. These are essentially research reactors or nuclear power plants with short operating times. About 70 per cent of the cases of children under 5 years of age living within the inner 5-km area included in the present study had already been included in the previous studies 1 and 2, and 80 per cent of cases in the previous studies are included in the current study. The discrepancy is due to the exclusion of a number of nuclear plants and also to the additional time span considered (1996-2003) and the modified definition of "vicinity". In the previous studies, communities were assigned a 5,10 or 15 km zone according to the location of most of their area, and no individual house coordinates were used.

Similar to the result of the main question of the previous study (age up to 15 years, 15-km area), the consideration of all malignancies in children of less than 5 living within the inner 5-km areas in the first studies did not lead to the conclusion that an increased risk existed because the effect estimates were not statistically significant (two-sided tests). However, using the approach of the present study, a statistically significant increase of risk was found (one-sided test).

The, at the time, most debated result obtained by exploratory data analysis in study 1 (relatively clear increase in the risk of acute leukaemia in children under 5 years of

age living within the 5-km area) is confirmed to a similar order of magnitude by the present study and on the basis of the extended time span of 1980-2003. As regards leukaemia, the influence of the previous results on the present results is very obvious. The risk estimate obtained in Study 1 for the period of 1980 to 1990 is nearly identical with that obtained for the same period in the present study. The odds ratio for the period after the two previous studies (1996-2003) is lower than that obtained for the preceding periods.

The former had been an exploratory result within Study 1 which was, therefore, less relevant than the confirmatory analyses within the same study. In the study which was intended to check this (Study 2) the significant result was not confirmed however the relative risk was increased. In the latest study the same question was examined as a secondary question, and this time a statistically significant result was obtained.

## Conclusions

The present study confirms that in Germany there is a correlation between the distance of the home from the nearest NPP at the time of diagnosis and the risk of developing cancer (respectively leukaemia) before the $5^{th}$ birthday. This study is not able to state which biological risk factors could explain this relationship. Exposure to ionising radiation was neither measured nor modelled. Although previous results could be reproduced by the current study, the present status of radiobiologic and epidemiologic knowledge does not allow the conclusion that the ionising radiation emitted by German NPPs during normal operation is the cause. This study can not conclusively clarify whether confounders, selection or randomness play a role in the distance trend observed.