

Exposure to Magnetic Fields and Survival after Diagnosis of Childhood Leukemia: A German Cohort Study

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Abstract

Inspired by a recent U.S. study showing poorer survival among children with acute lymphoblastic leukemia (ALL) exposed to magnetic fields above 0.3 μ T, we examine this relationship in a German cohort of childhood leukemia cases derived from previous population-based case-control studies conducted between 1992 and 2001. A total of 595 ALL cases with 24-h magnetic field measurements are included in the analysis with a median follow-up of 9.5 years. We calculate the hazard ratios (HR) using the Cox proportional hazards model for overall survival, adjusted for age at diagnosis, calendar year of diagnosis, and gender. Elevated hazards are found for

exposures between 0.1 and 0.2 μ T [HR, 2.6; 95% confidence interval (95% CI), 1.3-5.2], based on 34 cases with 9 deaths as well as for exposures above 0.2 μ T (HR, 1.6; 95% CI, 0.6-4.4), based on 18 cases with 4 deaths. After adjustment for prognostic risk group, the hazard for exposures above 0.2 μ T increases to HR, 3.0 (95% CI, 0.9-9.8). In conclusion, this study is generally consistent with the previous finding; however, we report the excess risk at field levels lower than those in the U.S. study. In all, the evidence is still based on small numbers, and a biological mechanism to explain the findings is not known. (Cancer Epidemiol Biomarkers Prev 2007;16(6):1167-71)

Introduction

The relation between exposure to extremely low-frequency magnetic fields and the risk of childhood leukemia has been examined in several studies. Most epidemiologic studies have shown a small increase in risk with higher exposures (above 0.3 or 0.4 μ T; ref. 1), but the overall evidence is still inconclusive because the association found in observational studies lacks both a plausible mechanism and supportive evidence from experimental studies (2). Recently, this was taken a step further by Foliart et al. (3); if exposure to magnetic fields is associated with increased leukemia incidence, it could also have a relationship with survival. Indeed, they reported a somewhat poorer survival among 412 U.S. childhood acute lymphoblastic leukemia (ALL) patients exposed to magnetic fields above 0.3 μ T compared with those exposed to magnetic fields below 0.1 μ T. However, due to small numbers of exposed children, the authors themselves characterized their study as only hypothesis generating. Here, we investigate this new hypothesis in a German cohort of 595 childhood ALL patients.

Materials and Methods

We use data on childhood leukemia and extremely low-frequency (ELF) magnetic fields from three different studies conducted previously in Germany (Table 1; refs. 4-6). They were all population-based case-control studies, with the cases identified through the German Childhood Cancer Registry (GCCR), which is estimated to be more than 95% complete (7). The cohort consisted of children <15 years old who were living in the relevant study area (see below) at the date of diagnosis. Magnetic field exposure levels were assessed by 24-h measure-

ments taken within each child's bedroom, and additional information on other risk factors or potential confounders was obtained from questionnaires. The first study covered Lower Saxony (northwestern part of Germany; population, 7.4 million) with children diagnosed during the period July 1988 to June 1993, and measurements done between November 1992 and July 1995 (4). The second study was conducted in Berlin and included children diagnosed between January 1991 and September 1994, with measurements done between November 1992 and mid-1996 (5). The third study covered the whole of former West Germany with children diagnosed between October 1992 and September 1994, plus an extra component of children living in the vicinity of German nuclear installations and diagnosed between January 1990 and September 1994. The measurements were done between November 1997 and December 1999 (6). A few children were eligible for more than one study. But once included in one study, the children were not included in any of the following studies. The response rates in the three studies varied from 59% to 66% of eligible children. The numbers of ALL cases contributed from each study are 108 (Lower Saxony), 38 (Berlin), and 449 (West Germany), for a total of 595 children.

Over 98% of German children with leukemia are treated in clinical trials. Follow-up of the patients established at the GCCR can be described as follows: during the first 5 years after the end of treatment, the GCCR receives follow-up information about the children from the clinical trial centers once a year. In a second phase, the GCCR asks the respective hospitals for information every 3 years. When the children are grown up and no longer connected to the pediatric hospitals, they are actively followed up by the GCCR by mail every 5 years for their entire lifetime. By all three mechanisms, the exact dates of an event (death, relapse, and secondary tumor) are obtained. In case no event occurred, the date of the last contact is recorded. For more details, see Kaatsch et al. (8). Effective February 2006, the longest follow-up was 16.4 years, and the median was 9.5 years.

To adjust for the stage of the disease, the cases are classified by prognostic risk groups, which was possible for children treated within the major clinical trials. Most German children with ALL are treated in the ALL-BFM (Berlin, Frankfurt, Münster) trials, which were initiated in 1976. The consecutive trials ALL-BFM 86 and ALL-BFM 90 recruited patients

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Table 1. Overview of the three original studies

Study	Lower Saxony	Berlin	West Germany
Children diagnosed between	July 1988 to June 1993	January 1991 to September 1994	January 1990 to September 1994
Measurements done between	November 1992 to July 1995	November 1992 to July 1996	November 1997 to December 1999
Number of children	108	38	449
Person-years of follow-up	1,160	299	3,953
Number of children with prognostic risk group	88	37	361
Children in standard-risk group	23	7	105
Children in medium-risk group	56	29	218
Children in high-risk group	9	1	38

between October 1986 and March 1995 (9, 10). Briefly, risk groups were divided into three categories. The standard-risk group had to fulfill all of the following six criteria: (a) a low score (<0.8) composed of absolute peripheral blast cells; (b) liver size and spleen size (calculated $0.2 \times \log(\text{blasts}+1) + 0.06 \times \text{liver size} + 0.04 \times \text{spleen size}$); (c) a peripheral blast count <1 G/L on day 8 after 1 week of prednisone therapy; (d) CR in the bone marrow on day 33 ($<5\%$ blasts in the bone marrow after regeneration with normal or nearly normal cellularity); (e) neither mediastinal tumor nor pre-T-/or T-immunology (TdT⁺, CyCD3⁺, CD7⁺; ref. 10); (f) no evidence of central nervous system involvement and no *t*(9;22) or BCR-ABL recombination. The median-risk group contained four items that had to be fulfilled: (a) a higher score as mentioned above (≥ 0.8); (b) peripheral blast count <1 G/L on day 8 after 1 week of prednisone therapy; (c) CR in the bone marrow on day 33; (d) no *t*(9;22) or BCR-ABL recombination. The high-risk group was characterized by one of the following: blast count more than 1 G/L on day 8 after 1 week of prednisone, *t*(9;22) or BCR-ABL, or no CR on day 33.

The information on risk groups is unfortunately only available from some hospitals. Thus, analyses including risk groups further restrict the sample to 88, 37, and 361 cases from Lower Saxony, Berlin, and West Germany, respectively, with a total of 486 cases of ALL (Table 1).

The relation between exposure to ELF magnetic fields and overall survival after the diagnosis of ALL was assessed using the Cox proportional hazards model adjusting for age, calendar year at diagnosis, and gender. Season of measurement, socioeconomic status (average or high), and type of residential area (rural, mixed, or urban) were examined as additional potential confounders but were not included in the final model. Cases were followed from the date of diagnosis until date of death (=event), and those alive at the end of the study period were censored at day of last contact. Analyses were conducted for the full cohort and for the sample with prognostic data stratified by risk group. As in our previous studies (4-6), the exposure metric was the median magnetic field of the 24-h bedroom measurement which was divided into three exposure categories: low, below 0.1 μT ; medium, from 0.1 to 0.2 μT ; and high, above 0.2 μT .

In addition, the study by Foliart et al. (3) was replicated as close as possible; we excluded children below 1 year of age and children who were not in remission and used the exposure groups <0.1 , 0.1 to 0.2, 0.2 to 0.3, and above 0.3 μT . For this approach, both an overall survival analysis and an event-free survival analysis (where death, relapse, and secondary tumor are considered events and cases were followed until the respective date of the first event or censored at day of last contact) with the same adjustment as above were done.

Results

Exposure and prognostic risk group did not seem to be associated, consistent with Foliart et al. (ref. 11; Table 2). The

Kaplan-Meier survival curve showed clear differences among the three magnetic field exposure groups (Fig. 1). For these unadjusted data, the survival was slightly better for the high exposed than for the medium exposed.

In the course of developing the analytic model for the adjusted risk estimates, the effect of the potential confounding factors (age at diagnosis, year of diagnosis, gender, socioeconomic status, type of residential area, season of measurement) was assessed in an overall survival analysis restricted to the low-exposure group only (<0.1 μT). The effect of age was modeled as a spline; the hazard decreased rather steeply up until the age of 3 years, with hazard ratios (HR) of 0.6 [95% confidence interval (95% CI), 0.4-1.0] per year, and from there on, it increased slightly, HR, 1.1 (95% CI, 1.0-1.2) per year. Year of diagnosis was included as a linear variable, and there was some decrease in hazard over time, HR, 0.9 (95% CI, 0.8-1.1) per year. Gender showed a tendency with girls having a better survival than boys, HR, 0.6 (95% CI, 0.3-1.1). Neither socioeconomic status, type of residential area, or season of measurement had a relevant impact. Consequently, age, calendar year of diagnosis, and gender were included in the main analyses.

The adjusted results are shown in Table 3. For the subcohort with stratification for risk group, the respective HRs were 2.8 (95% CI, 1.2-6.2) for medium and 3.0 (95% CI, 0.9-9.8) for high exposure based on 7 and 3 deaths, respectively. For a trend analysis using magnetic field as a continuous variable, the estimated HR was 1.4 (95% CI, 1.0-1.8) per 0.1- μT increment (Table 2); in this analysis with exposure as a continuous variable, any measurement below 0.1 μT was set to be 0.05 μT because this was considered a reasonable detection limit.

For the entire cohort without stratification, we computed adjusted HRs of 2.6 (95% CI, 1.3-5.2) for the medium-exposure group and 1.6 (95% CI, 0.6-4.4) for the high-exposure group, whereas the HRs for the subcohort without stratification were 2.4 (95% CI, 1.1-5.2) and 2.1 (95% CI, 0.7-7.0) for the medium- and high-exposure groups, respectively.

The replication of Foliart's analytic model (3) included a total of 460 cases and resulted in HRs for overall survival of 3.1 (95% CI, 1.3-7.3), 2.7 (95% CI, 0.4-20.2), and 2.8 (95% CI, 0.4-20.6) for the exposure groups 0.1 to 0.2, 0.2 to 0.3, and above 0.3 μT , respectively, based on 6, 1, and 1 deaths. For the event-free survival, the corresponding HRs were 2.2 (95% CI, 1.0-4.5), 1.5 (95% CI, 0.2-11.2), and 1.4 (95% CI, 0.2-9.9) based on 8, 1, and 1 events.

Table 2. Relation between prognostic risk group and exposure

Risk group	Exposure		
	Low, <0.1 μT	Medium, 0.1 to <0.2 μT	High, ≥ 0.2 μT
Standard	122	10	3
Medium	277	17	9
High	46	2	0

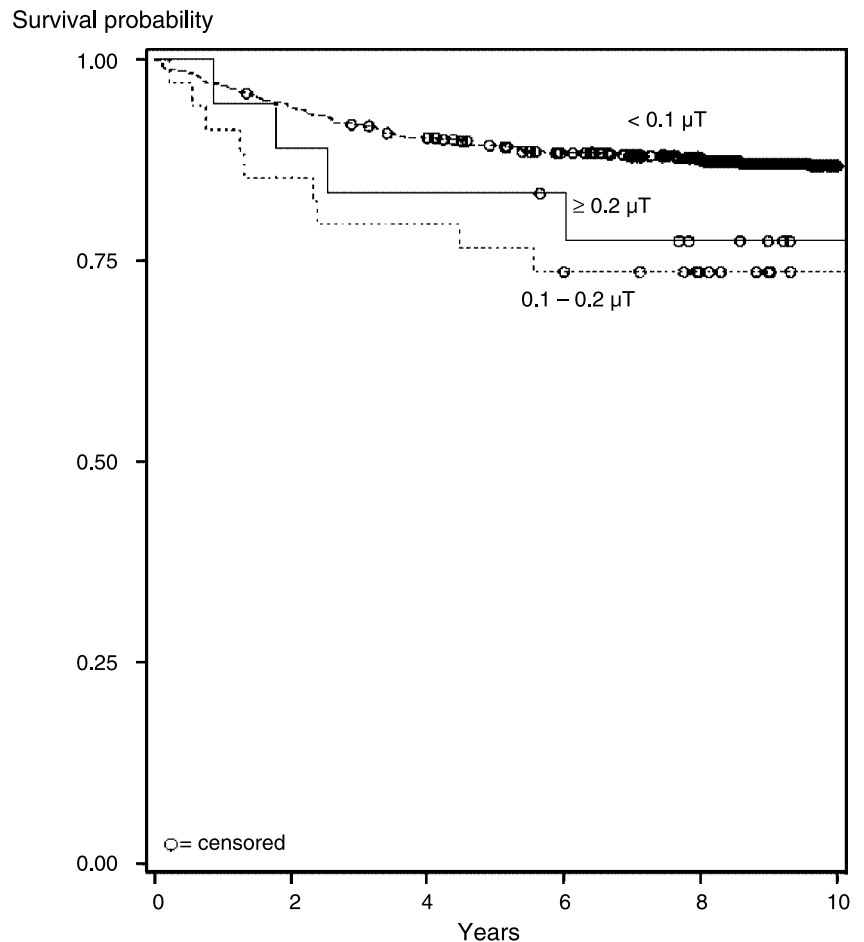


Figure 1. Survival distribution as a function of years since diagnosis for the three groups of exposure to magnetic fields separately.

Discussion

Our main finding is an elevated risk of survival failure among childhood ALL cases in the medium (0.1-0.2 μT) and high ($>0.2 \mu\text{T}$) magnetic field exposure groups. With stratification for prognostic risk group, the highest risk appears for the highest exposure group, whereas without stratification, it appears for the medium-exposure group. Thus, there is a tendency for the HRs to increase with increasing exposure, although it does not seem to be linear. Being the predictor of survival, the stratification for prognostic risk group is justified though it reduces the data material, and to illustrate the effect of excluding subjects with unknown risk group, we present the unadjusted HRs for both the full cohort and the subcohort.

A similar trend was reported by Foliart et al. (3), but they only reported increased survival failure for cases classified with magnetic field levels above 0.3 μT ; in our study, excess risk appears with exposure levels above 0.1 μT . Apart from differences in the assessment of exposure, the main differences between the studies concern participation rate and duration of follow-up. The study by Foliart had a 29% participation rate, with the lowest rate among non-White children. Moreover, a higher percentage of non-White children than of White children were classified with high exposure. Thus, in their study population, the high exposed (non-White) children may have been underrepresented, thereby decreasing the power of the study. In our study with the median follow-up of 9.5 years, 83% of the failure events happened within the first 5 years after diagnosis, which can also be seen from Fig. 1. The Foliart study had a median follow-up of 5.07 years, so they might have missed some failure events if their data had been similar to ours, which could affect the result in either direction. The prognostic risk groupings also differ as to how they are

defined in the German and U.S. ALL clinical trials. Foliart et al.'s (3) primary exposure metric was the mean personal field level logged over a 24-h period in the weeks following enrollment. Our study used the median 24-h bedroom measurement within a few years after diagnosis. In the Foliart study, the families did the measurements themselves according to the protocol received from the investigators, whereas in our study, they were done by professionals according to a standardized protocol.

Our finding of improved survival over time for year of diagnosis is well in accordance with the existing literature (12). As for the dependence on age, it is known that the very young (below 1 year of age) and the group aged 10 to 14 have the poorest survival, but other than that, survival is only considered by 5-year age groups (12). Making the reasonable assumption that age-specific survival is a smooth curve, this still offers support for our finding of the simplified spline with the knot at age 3 years. The poorer survival of boys than of girls, although not significant, is also in agreement with findings in previous survival studies (12). These findings support the validity of our statistical model and the representativeness of our study population.

As an alternative to follow the children from date of diagnosis, we also did similar analysis following the ones who reached remission from that point forward. The results did not change (data not shown).

In this study, we had a participation rate of $\sim 60\%$, and this could introduce a bias. It could be that mainly the ones living beneath power lines (and who are worried about this) choose to participate. This would result in a larger proportion of our study group being in the high-exposure group, and having many highly exposed would only increase the power of the study but not introduce a bias. Another concern could be that

Table 3. Association of magnetic field exposure and childhood leukemia survival

Subgroup*				
With stratification for risk group				
Exposure	Cases	Events	Person-years	HR [†] with CI
Total	486	65	4,356	
<0.1 μ T	445	55	4,016	1
0.1 to <0.2 μ T	29	7	247	2.8 (1.2-6.2)
\geq 0.2 μ T	12	3	93	3.0 (0.9-9.8)
Continuous, [‡] HR per 0.1 μ T				1.4 (1.0-1.8)
Subgroup*				
No stratification for risk group				
Exposure	Cases	Events	Person-years	HR [†] with CI
Total	486	65	4,356	
<0.1 μ T	445	55	4,016	1
0.1 to <0.2 μ T	29	7	247	2.4 (1.1-5.2)
\geq 0.2 μ T	12	3	93	2.1 (0.7-7.0)
Total cohort*				
No stratification for risk group				
Exposure	Cases	Events	Person-years	HR [†] with CI
Total	595	83	5,412	
<0.1 μ T	543	70	4,978	1
0.1 to <0.2 μ T	34	9	281	2.6(1.3-5.2)
\geq 0.2 μ T	18	4	154	1.6(0.6-4.4)

*Subgroup is all subjects of the total cohort, for whom information on prognostic risk group was available.

[†] Hazard ratios from Cox proportional hazards model with adjustment for age at diagnosis, calendar year of diagnosis, and gender, with and without stratification by risk group.

[‡] In the continuous analysis, any exposure below 0.1 μ T was set to be 0.05 μ T because we consider this to be a reasonable detection limit of an accurate measurement.

low social class patients have both poorer survival and higher exposures. We do not believe that this is a great concern for the German study, due to the German health care system of free and equal access, and also supported by the observation that adjusting for socioeconomic status had no impact on the results. It could also be reasonable to expect that the degree of illness of the child influences participation. A proxy for this is prognostic risk group. As shown in Table 1, the distribution of risk groups is similar for all three exposure categories. One word of warning, however, is that this is based on small numbers. The largest group (the low-exposure group) is distributed with 27% of patients in the standard-risk group, 62% in the medium-risk group, and 10% in the high-risk group. This is well in line with the distribution found in a large clinical trial ($n = 2,178$; ref. 10), where the same groups contain, respectively, 29%, 60%, and 11%, offering support to the viewpoint that there is no selection bias. Other strengths of the study are that the exposure assessment is based on objective measurements, and that the follow-up is long enough as can be seen from the Kaplan-Meier curve (Fig. 1).

A weakness of our study is that the study material was collected for another purpose than the analyses presented here. This in particular means that the measurement of magnetic fields was done after diagnosis, but in the house where the child lived longest before diagnosis. Thus, the exposure could have been assessed in a house where the child no longer lived. For 75% of our cohort, we had information about mobility before diagnosis. Out of these children, 96% had lived in the same place a year before diagnosis, as where the measurements were later done. Thus, the study population is not very mobile, so for most children, the exposure was assessed in the

residence where they also lived after diagnosis. Some misclassification cannot be ruled out, but there is no reason to believe that it would be differential. Even in the case where one child who died from leukemia was wrongly placed in the medium exposure group instead of in the reference group, this would only change the HR for the medium-exposure group to a value between 2.3 and 2.6, depending on which one of the events was misclassified. So although the number of events in the medium category is low, the unlikely event of one of these events being misclassified does not explain our findings. Another weakness is that we consider overall survival, instead of leukemia-specific survival, but the cause of death is not systematically recorded in the clinical trial databases. However, given that our cohort consist of (German) children, any other cause of death is not likely, and out of 82 patients for whom cause of death was recorded, only one had a cause of death not related to the disease. A competing cause of death is death from a secondary tumor. It could obviously be debated how these deaths should be treated because most likely, they are treatment related. They are included in our analysis because our outcome of primary interest is overall survival. But only seven children, all in the reference group, have a secondary tumor. Four of these children died during the follow-up period. If they were excluded from the analysis, this would increase the HRs. The seven deaths in the medium exposure category occurred between the age of 4 and 14 years. Even if one of these deaths was not due to leukemia, then this would only change the result to a HR between 2.3 and 2.4 for the medium-exposure group, depending on which one of the seven deaths it was.

After adjusting for confounders, we observed elevated HRs of survival from childhood ALL associated with exposure to magnetic fields. Selection bias is likely to be a minor problem compared with previous case-control studies that have addressed the association of leukemia with magnetic fields (1). There is at present no biological explanation as to how exposure to magnetic fields could increase the risk of leukemia. However, if this is the case, exposure to magnetic fields might also increase the risk of relapse or failure of treatment and thereby decrease survival. However, in our study and in the previous one (3), the association between survival failure and magnetic fields was stronger in the overall survival analysis than in the event-free survival analysis. Possible explanations could be that exposure to magnetic fields has a higher impact on the risk of death than on the risk of relapse, that exposure to magnetic fields shortens the time from relapse to death, or that it is just a reflection of random variation due to small numbers.

In conclusion this study's results are broadly consistent with Foliart et al. (3) in that poorer survival among childhood ALL patients occurred in children in the higher exposure categories. However, the HRs here were seen at lower field levels than in the U.S. study. In all, the evidence is still based on small numbers, and a biological mechanism to explain the findings is not known.

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