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Original Paper

Magnetic Fields and Childhood Cancer—a Pooled Analysis of Two Scandinavian Studies

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To test the hypothesis that exposure to magnetic fields, of the type generated by high voltage installations, increases cancer incidence in children, the original data from two case–control studies were pooled. The Swedish study was based on children living within 300 m from transmission lines, and the Danish study on the total population of Denmark. In both these studies, national cancer registries were used to identify cases of leukaemia, lymphoma or central nervous system tumour. Controls were selected randomly from the study populations. Magnetic field exposure was assessed through theoretical calculations of the magnetic fields before the time of diagnosis. An elevated relative risk of childhood leukaemia was found for calculated magnetic field levels of ≥0.2 μT, estimated at 2.0 (95% CI 1.0–4.1), and for magnetic field levels of ≥0.5 μT, estimated at 5.1 (95% CI 2.1–12.6). The results support the hypothesis of an association between magnetic fields and childhood leukaemia.

Key words: child, electromagnetic fields, leukaemia, neoplasms, pooled analysis
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INTRODUCTION

SINCE THE first study suggesting a link between residential exposure to 50–60 Hz magnetic fields and childhood cancer was published by Wertheimer and Leeper [1] in 1979, additional epidemiological and experimental studies have followed [2–11].

During 1993, results from two Scandinavian case–control studies investigating the relationship between residential magnetic fields from power lines and childhood cancer were published [8, 10]. Both studies found elevated relative risks of leukaemia among children exposed to magnetic fields, and one study also found an elevated risk of lymphoma [8]. The studies took advantage of the population registry system in the Scandinavian countries which made it possible to minimize the risk for selection bias. They also used a novel approach to exposure assessment, in that magnetic fields were calculated based on power line configuration and load on the power lines for different points in time before diagnosis. However, both studies have limited numbers. Since we believe that random rather than systematic errors are the major reason for any differences in the relative risk estimates between the studies, the primary data from the two studies were combined in order to increase the number of exposed cases and obtain more stable relative risk estimates. This also provided an opportunity to use cumulative magnetic field exposure.

A Finnish study [9], published at the same time as the other two studies, could not be included in a pooled analysis because it was designed as a cohort study, while the others were case–control studies.

MATERIALS AND METHODS

Details on the Materials and Methods in the two studies are available in the original papers [8, 10]. Only a brief description of the studies will be given here.

Study base

The Swedish study base consisted of everyone under the age of 16 who had lived on a property at least partly located within 300 m from any of the 220 and 400 kV power lines in Sweden during the period 1960–1985, who were followed from their entry into the area through to 1985. Approximately 127 000 children were identified. Cases of cancer were identified through a record linkage to the Swedish cancer registry. Four controls per case were selected at random from the individuals in the study base. For each case, the controls were selected from those who were included in the study base during the year of diagnosis of the subject and were born in the same year, were of the same sex, lived in the same parish in the year of diagnosis or the last

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year before moving out of the area, and lived near the same power line as the case. To be comparable with the Danish study, the Swedish study has been restricted to leukaemia, lymphoma and central nervous system tumour cases in the analyses presented here.

The Danish study base consisted of the total population of Denmark under the age of 15, followed from 1968 through to 1986. Cases of leukaemia, malignant lymphoma and central nervous system tumour were identified from the Danish cancer registry. 2–5 controls per case were selected at random from the Danish central population register. Controls were selected among people who had survived without cancer until the date of diagnosis of the case, but matched the case on sex and date of birth (within 1 year). The main difference between the two study bases is that the Danish study includes the total population of Denmark, while the Swedish study includes only people living within a specified distance from power lines. Thus, the total number of cases is larger in the Danish study, but the number of exposed cases is larger in the Swedish study.

Exposure assessment

Exposure was defined as the magnetic fields generated by power lines or other high voltage installations close to the house. No attempt was made to estimate exposure from internal sources in the house.

In the Swedish study, magnetic field exposure was assessed by means of theoretical calculations of the magnetic fields in the home generated by the power lines. The calculations were based on detailed information about the power line configuration, distance between the power line and the house, and average load on the power line for the year closest in time before diagnosis and 1, 5 and 10 years before diagnosis, and at the time of birth and conception. All types of power lines within 300 m of the house were included in the calculations, with the exception of underground cables. Information on the historical load on the 220 and 400 kV power lines was available from detailed records of the operation of the different lines. The basic measure of exposure was the average magnetic field level generated by power lines in the year closest in time to diagnosis. Cumulative exposure was calculated based on information on the number of years a subject had been living close to a power line and the estimated magnetic field exposure for the different points in time before diagnosis, and was defined as the sum of the exposure for each year from conception to diagnosis, measured in μT-years. For years not spent within the power line corridor, the magnetic field level was estimated to be zero.

In the Danish study, for each address that a case or corresponding control had occupied, all 50–400 kV transmission connections (overhead lines or underground cables) and substations were identified. Calculations of magnetic fields were made for subjects with any high voltage electrical installation close to the house, based on information on the configuration of the installation, distance between the installation and the house and annual average load. Information on the load on the installations was in the form of estimates by people experienced in the planning and operation of the Danish transmission system [12]. The basic measure of exposure was the average magnetic field levels generated from high voltage installations to which the child was ever exposed. In addition, cumulative exposure was calculated by multiplying the number of months exposed by the average level of magnetic field at the residence. For children without any high voltage electrical installation close to the house, the magnetic field level was estimated as zero.

The definition of the exposure in the Swedish study as closest in time before diagnosis differs somewhat from the Danish definition. However, both studies aimed to estimate the exposure that occurred before diagnosis, based on detailed information about power line configuration and load.

The greatest emphasis was placed on the annual average historical fields, because they corresponded to the exposure estimates that have been used in previous studies. Analyses were made for several different cut-off points. Presented here are results for the cut-off points 0.1 and 0.2 μT, comparable to the original Swedish study, and also to the study by Savitz and associates [5]. Analyses of higher cut-off points were also made, and presented here are the results for the cut-off point 0.5 μT. This level was chosen because it was higher than the cut-off point used in the original Danish study, and at higher cut-off points the number of exposed subjects became too small. For cumulative exposure, the cut-off points 0.1 and 1.0 μT-years were chosen. For higher cut-off points, the number of exposed cases is small.

Statistical methods

Association between exposure and disease was measured by the incidence rate ratio, referred to in the text as the relative risk, and estimated through the odds ratio. The random variability was assessed by 95% confidence intervals (CI). All unmatched analyses were stratified by age (in 5 year groups), sex, and country and were performed with the logistic regression model [13]; the entire set of controls was used in the unmatched analyses. Matched analyses were carried out using conditional logistic regression.

RESULTS

Table 1 shows the number of cases and controls in the two studies. It is evident from this table that the number of cases in the Danish study is much larger than in the Swedish. However, since they are based on different populations, the distribution of the exposure differs between the two studies; in the Swedish study, 17% of the subjects are exposed to magnetic field levels of 0.1 μT or more, while in the Danish study, 0.5% of the subjects are so exposed. Thus, the number of exposed cases is larger in the Swedish study, in spite of the smaller total number of cases.

Table 2 displays the relative risk estimates for the Swedish and Danish study separately, and for the two studies combined, adjusted for age and sex, and in the combined analysis also for country. Results are presented for leukaemia, lymphoma and central nervous system tumours separately, and for all three diagnostic groups combined. Both the individual studies and the

Table 1. Cases of cancer and controls in the Swedish and Danish studies

	Sweden	Denmark	Combined study
	No.	No.	No.
Leukaemia	39	833	872
Lymphoma	19*	250†	269
Central nervous system tumour	33	624	657
Controls	558	4788	5356

*Three Hodgkin's disease, 16 non-Hodgkin's lymphoma. †84 Hodgkin's disease, 166 non-Hodgkin's lymphoma.

Table 2. Cancer risk in relation to calculated historical magnetic fields adjusted for age, sex and country

		Swedish study				Danish study				Combined study			
Diagnosis	μT	No. Cases	No. Controls	RR	95% CI	No. Cases	No. Controls	RR	95% CI	No. Cases	No. Controls	RR	95% CI
Leukaemia	≤0.09	27	475	1		829	4768	1		856	5243	1	
	0.1–0.19	4	33	2.6	0.8–8.1	1	5	1.2	0.1–10.3	5	38	2.0	0.7–5.3
	≥0.2	7	46	2.7	1.1–6.6	3	15	1.3	0.4–4.6	10	61	2.0	1.0–4.1
	0.1–0.49	6	62	1.9	0.8–5.0	1	18	0.4	0.0–2.8	7	80	1.2	0.5–2.7
	≥0.5	5	17	4.6	1.5–13.8	3	2	8.1	1.3–49.8	8	19	5.1	2.1–12.6
Lymphoma	≤0.09	16	475	1		247	4768	1		263	5243	1	
	0.1–0.19	1	33	0.9	0.1–6.9	0	5	0		1	38	0.7	0.1–5.6
	≥0.2	2	46	1.3	0.3–5.9	3	15	3.3	0.9–11.5	5	61	2.1	0.8–5.5
	0.1–0.49	2	62	0.9	0.2–4.2	2	18	1.9	0.4–8.3	4	80	1.3	0.4–3.7
	≥0.5	1	17	1.9	0.2–15.2	1	2	8.7	0.8–99.6	2	19	3.3	0.7–15.0
Central	≤0.09	29	475	1		621	4768	1		650	5243	1	
nervous	0.1–0.19	2	33	0.8	0.2–3.6	1	5	1.4	0.2–12.2	3	38	1.1	0.3–3.6
system	≥0.2	2	46	0.7	0.2–3.2	2	15	1.0	0.2–4.3	4	61	0.8	0.3–2.4
tumour	0.1–0.49	3	62	0.7	0.2–2.4	1	18	0.4	0.1–3.0	4	80	0.6	0.2–1.8
	≥0.5	1	17	1.1	0.1–8.8	2	2	7.8	1.1–55.7	3	19	2.3	0.6–8.0
Combined	≤0.09	72	475	1		1697	4768	1		1769	5243	1	
group	0.1–0.19	7	33	1.4	0.6–3.2	2	5	1.1	0.2–5.9	9	38	1.4	0.6–2.9
	≥0.2	11	46	1.6	0.8–3.2	8	15	1.5	0.6–3.6	19	61	1.5	0.9–2.7
	0.1–0.49	11	62	1.2	0.6–2.3	4	18	0.7	0.2–1.9	15	80	1.0	0.6–1.8
	≥0.5	7	17	2.7	1.1–6.8	6	2	8.1	1.6–40.2	13	19	3.5	1.7–7.3

RR, relative risk; CI, confidence interval.

combined material show elevated relative risk estimates for leukaemia. In the combined data set it is estimated at 2.0 (95% CI 0.7–5.3) and 2.0 (95% CI 1.0–4.1) for the exposure categories 0.1–0.19 μT and ≥0.2 μT, respectively. Increasing the cut-off point tends to increase the relative risk estimate. Thus, the relative risk is estimated at 5.1 (95% CI 2.1–12.6) for magnetic field levels of ≥0.5 μT. It is important to note that the results are not dependent on the choice of cut-off point. For each increase in the exposure above 0.2 μT, the relative risk increases correspondingly (data not shown). For lymphoma, there is an elevated relative risk for very high exposure levels in both the individual studies, but it is based on very small numbers. The 3 cases in the exposure category ≥0.2 μT in the Danish study all had Hodgkin's disease, while the 2 cases in the same exposure category in the Swedish material were all diagnosed as non-Hodgkin's lymphoma. For central nervous system tumours, there was no evidence of an association in the Swedish study. The Danish study showed elevated relative risk estimates for high exposure levels, but based on very small numbers. Nevertheless, an elevated relative risk for the exposure level ≥0.5 μT is observed in the combined material, but is based on only three exposed cases.

The mean exposure for subjects belonging to the category ≥0.2 μT was 0.53 μT, and the median exposure 0.39 μT. Defining exposure as cumulative lifetime exposure, shown in Table 3, did not change the results. An elevated relative risk estimate was found for leukaemia in the highest exposure category. For lymphoma, the relative risk estimate was elevated in the intermediate exposure category, but not in the highest. There were, however, only 2 exposed cases in the highest exposure category. No evidence of an association was found for central nervous system tumours. If a higher cut-off point for the exposure was chosen, the relative risk of leukaemia increased, but the number of exposed cases became small (data not shown).

The risk estimates from the matched analyses did not differ significantly from the unmatched, but the confidence intervals were wider owing to the inability to use all controls in the matched analyses (e.g. for leukaemia, the relative risk for the exposure category ≥0.2 μT was 1.8, 95% CI 0.7–4.6; and for the exposure category ≥0.5 μT the relative risk was 5.4, 95% CI 1.5–18.9).

DISCUSSION

The main finding of the combined study was an elevated relative risk for childhood leukaemia in relation to calculated historical magnetic fields, which increases with level of exposure. The Danish finding of an elevated relative risk for lymphoma was confirmed in the combined study, but still based on very small numbers. In the Danish study, all exposed lymphoma cases were diagnosed as Hodgkin's disease. This finding was not confirmed in the Swedish material, where all exposed cases were diagnosed as non-Hodgkin's lymphoma. For central nervous system tumours, an association was found only in the Danish study, and only for very high exposure levels. Combining the two studies yielded an elevated relative risk, but this was still based on small numbers.

Using cumulative exposure did not add much to the understanding of the association between magnetic fields and cancer in this study. The number of exposed cases was too small, even in the combined material, to allow for the evaluation of cumulative exposure differentiated from other measures of exposure. The exposed cases using cumulative exposure tend to be the same as the exposed cases, using the estimated exposure closest in time to diagnosis.

Table 3. Cancer risk in relation to cumulative lifetime magnetic field exposure, adjusted for age, sex and country

		Swedish study				Danish study				Combined study			
Diagnosis	μT-years	No. Cases	No. Controls	RR	95% CI	No. Cases	No. Controls	RR	95% CI	No. Cases	No. Controls	RR	95% CI
Leukaemia	≤0.09	21	336	1		829	4760	1		850	5096	1	
	0.1–0.9	11	180	1.4	0.6–3.0	1	18	0.4	0.0–2.7	12	198	0.9	0.5–1.8
	≥1.0	6	38	3.6	1.3–9.8	3	10	1.9	0.5–7.1	9	48	2.5	1.1–5.4
Lymphoma	≤0.09	10	336	1		245	4760	1		255	5096	1	
	0.1–0.9	8	180	1.3	0.5–3.5	4	18	4.0	1.3–11.8	12	198	2.0	0.9–4.3
	≥1.0	1	38	0.8	0.1–6.5	1	10	1.7	0.2–13.1	2	48	1.2	0.3–5.3
Central nervous system tumour	≤0.09	18	336	1		621	4760	1		639	5096	1	
	0.1–0.9	14	180	1.2	0.6–2.5	1	18	0.4	0.1–3.1	15	198	1.2	0.6–2.2
	≥1.0	1	38	0.4	0.0–3.0	2	10	1.5	0.3–6.8	3	48	0.8	0.2–2.7
Combined group	≤0.09	49	336	1		1695	4760	1		1744	5096	1	
	0.1–0.9	33	180	1.3	0.8–2.1	6	18	1.0	0.4–2.4	39	198	1.2	0.8–1.9
	≥1.0	8	38	1.5	0.6–3.4	6	10	1.7	0.6–4.7	14	48	1.6	0.8–2.9

*RR, relative risk; CI, confidence interval.

Each of the two studies taken separately has limited numbers. By combining the studies, it is possible to obtain more precise relative risk estimates, and also provides an opportunity to analyse higher levels of exposure. A prerequisite for combining epidemiological studies is that the studies are sufficiently similar for the assumption that random error is the main reason for differences in the results between the studies. We conclude that the Swedish and Danish study are similar enough to perform a meta-analysis. The design of each study and the conditions for conducting epidemiological studies were similar in both countries. Both studies took advantage of the population registry system in the Scandinavian countries and the nationwide cancer registries, thereby minimising the risk for selection bias. Furthermore, exposure assessment was quite similar in both studies, using historical calculated magnetic fields generated by power lines as the basic measure of exposure. There were certain differences in the primary data, e.g. how historical loads on the power lines were estimated, or whether underground cables were included, but we postulate that the assessment of the exposure is similar enough to be combined in a meta-analysis.

Since the results from the matched and the unmatched analyses did not differ significantly, only the unmatched analyses were presented. In the pooled analyses, all available controls were used for each tumour subgroup; thus, the analyses differ from the ones used in the Danish study. This implies that potential confounding effects of age and sex were controlled for by use of multiple regression methods rather than through the original matched design. However, the advantage of a reduced variability seems to compensate for possible drawbacks in the unmatched estimates.

None of the studies have taken other sources of magnetic field exposure into account. However, there is no reason to believe that misclassification of the exposure due to other sources would differ between cases and controls. Hence, such misclassification would lead to a dilution of the true effect and cannot explain the observed association between childhood leukaemia and magnetic field exposure.

Control of confounding factors from socioeconomic status was employed in both the original studies; of car exhaust, county, type of building and year of diagnosis in the Swedish study; and of population density and number of changes of address in the Danish study. None of these variables changed the results. Hence, no control of confounding factors was made in the joint analysis, except for the variables, age and sex. Confounding factors could be an explanation for the observed association between magnetic fields and childhood leukaemia, but then it would have to be confounding from some hitherto unknown risk factor closely related to magnetic field exposure.

In spite of the combination of data from two different studies, numbers were still small, especially in the highest exposure categories, or when several levels of exposure were analysed. We analysed higher exposure levels than those made in the two original studies, showing stronger effects for higher levels of exposure. However, the small number of exposed cases makes it difficult to draw firm conclusions about the shape of any dose–response pattern. The results indicate that a focus on highly exposed subjects in future studies is warranted. Support for this is also provided by a re-analysis of the data from the study by Savitz and associates [5, 14], where larger odds ratios were found using higher cut-off points for the exposure. Furthermore, all studies using wire configuration codes to assess the exposure, except the Fulton study, showed higher effect estimates for the highest exposure category [1, 2, 5, 7]. There is a problem in finding a sufficiently large population of highly exposed children. Choosing lower cut-off points for the exposure might lead to false negative conclusions.

The potential public health impact of exposure to magnetic fields is not possible to assess. To date, there is no known mechanism by which the magnetic field interacts with biological systems and knowledge is also limited concerning the relevant exposure measure, and disease outcomes. Restricting the discussion to childhood leukaemia and to exposure from high-voltage installations (in Sweden 220 and 400 kV power lines) limits the effect on public health to less than one extra case per year in Sweden and Denmark.

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