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Magnetic fields and leukemia — risk for adults living close to power lines

by Pia K Verkasalo

Department of Public Health
PO Box 41
(Mannerheimintie 12)
FIN-00014 University of Helsinki
Finland

Supervisors

Associate Professor Jaakko Kaprio
Department of Public Health
University of Helsinki
Helsinki, Finland

Professor Markku Koskenvuo
Department of Public Health
University of Turku
Turku, Finland

Professor Lyly Teppo
Finnish Cancer Registry
Institute for Statistical and Epidemiological Cancer Research
Helsinki, Finland

Reviewers

Professor Anders Ahlbom
Institute of Environmental Medicine
Karolinska Institutet
Stockholm, Sweden

Docent Jarmo Virtamo
Department of Nutrition
National Public Health Institute
Helsinki, Finland

To

Pekka, Roosa, Veera and Sonja

Abstract

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The objective of this study was to investigate the risk of leukemia from magnetic field exposure among Finnish adults living close to high-voltage power lines. The cohort study included 383 700 Finnish people having lived in 1970—1989 within 500 m of overhead power lines of 110—400 kV in a magnetic field calculated to be ≥ 0.01 μT. The nested case-cohort study was conducted to investigate dose-response and time-related factors in further detail. Data collection was based on several subsequent record linkages of nationwide registers. The subjects were followed for cancer in 1974—1990, providing over 2.5 million person-years. The outcome measures included standardized incidence ratios, incidence rate ratios, and odds ratios for several exposure indices. The total number of leukemia cases was 203. Magnetic fields were not associated with the overall occurrence of leukemia among adults. The risk estimates were adjusted for age, gender, and municipality; the other covariates had no effect on the risk estimates. However, an almost fivefold increase with statistical significance was observed for the risk of chronic lymphatic leukemia in relation to earlier, or long-lasting, exposure to magnetic fields of ≥ 0.1 μT. This finding was based on very small numbers. No risk increases were observed for other types of leukemia. While the possibility of an increase in risk at higher magnetic field levels, or in relation to earlier exposures, cannot be excluded on the basis of this study, the results suggest that typical magnetic fields of high-voltage power lines are not an important cause of leukemia in adults.

Key terms electromagnetic fields, epidemiology, sociodemographic factors.

Abbreviations

ALL	Acute lymphatic leukemia
AML	Acute myeloid leukemia
CI	Confidence interval
CLL	Chronic lymphatic leukemia
CML	Chronic myeloid leukemia
ELF	Extremely low frequency
IARC	International Agency for Research of Cancer
ICD-7	International Classification of Diseases, 7th revision (1955)
IRR	Incidence rate ratio
OR	Odds ratio
PMR	Proportionate mortality ratio
RR	Relative risk
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio

Introduction

The planning of a new power line often evokes great concern about the possible health hazards related to living near the line. The question of the possible carcinogenic effect of magnetic fields was, likewise, first raised in the 1970s in Denver in the United States where a cluster of childhood cancers was suspected among children living close to power lines. In 1979, Wertheimer & Leeper (1) published the results of an epidemiologic study indicating a threefold increase in the overall cancer risk of Denver children living near the lines. This was the actual beginning of multidisciplinary research consisting of epidemiologic studies, exposure characterization and laboratory experiments, centering around the question of the influence of 50—60 Hz extremely low-frequency (ELF) magnetic fields on carcinogenesis. The epidemiologic research has included cancers in both children and adults, and exposures from residential and occupational sources have been considered.

The Finnish study on residential magnetic fields and adult cancer began in 1988. At that time, there were only four power-line studies on childhood cancer and three on adult cancer. Nine more studies have later been published on magnetic fields and childhood cancer and three more on adult cancer and some large studies on childhood cancer are still ongoing in Europe. A third epidemiologic research topic, that of adult cancer in relation to occupational sources of magnetic fields, has also appeared. The methodology used for these three areas of epidemiologic research has improved immensely. While the earlier studies may have been susceptible to control-selection biases or had no information available on person-years at risk, the more recent studies have applied more proper study designs. The greatest advancements have, however, occurred in the assessment of exposure to magnetic fields.

It has become more and more apparent that power lines are only one of several sources of magnetic fields and that man-made magnetic fields are ubiquitous in modern society. Magnetic field is a time-dependent vector quantity with a magnitude and direction. Since there is a variety of magnetic field sources, assessments of exposures to magnetic fields should, ideally, take into account the numerous components of magnetic fields from all sources affecting the observation point at that particular instant in time. Exposure assessment becomes even more complicated when the issue is to estimate exposures over periods of several years, or even decades. Two alternative approaches have dealt with the problems related to the magnitude and timing of exposure. Some studies have focused on the magnitude aspect and have actually measured the fields with portable dosimeters, whereas others have placed more emphasis on the stability of exposure over time and have identified a dominating field source. Whichever the case, it is the presence of exposure differentials within the study population that is an elementary prerequisite for an epidemiologic study. Any knowledge of absolute exposure levels is — from the epidemiologic point of view — only of secondary importance.

Despite the fact that there are hundreds of laboratory experiments and a few prevailing biological hypotheses, the possible carcinogenic mechanism of magnetic fields has remained in essence unknown. In this avenue of research, however, epidemiology and biological plausibility are two closely intertwined issues. The results of epidemiologic studies would need stronger support from biological studies to be generally accepted as evidence for genuine public health risk. On the other hand, the inspiration of laboratory experiments has come primarily from the epidemiologic studies. The purpose of the present study was to investigate the risk of leukemia among Finnish adults exposed to the magnetic fields of high-voltage power lines with special emphasis on time-related factors.

Review of the literature

Magnetic fields

Definition

Several comprehensive publications now exist on the characteristics of environmental electric and magnetic fields. This and the following two sections are largely based on a review by Deno & Carpenter (2). The term "extremely low-frequency (ELF) electromagnetic fields" refers to the electromagnetic spectrum belonging to the frequencies of 30—300 Hz. In these frequencies, according to Deno & Carpenter (2), the electric and magnetic fields are usually analyzed more appropriately as separate and slowly time-varying electric or magnetic energy fields, as opposed to frequencies above 100 kHz, where they should be analyzed as coupled electromagnetic fields.

A magnetic field is a form of stored energy. Magnetic field strength is a vector quantity with a magnitude and direction at an instant time, and it is denoted by H in units of ampere per meter ($A \cdot m^{-1}$). The magnetic field comes from the motion of charge (I, current flow). Accompanying the magnetic field is the magnetic flux density vector B in teslas (1 mG is equal to 0.1 µT) which is — as opposed to the former — a directly measurable quantity. The connection between magnetic flux density and magnetic field strength is $B = \mu H$, where the symbol µ denotes permeability (ie, the magnetic property of the material). Later in this study, B is referred to as magnetic field.

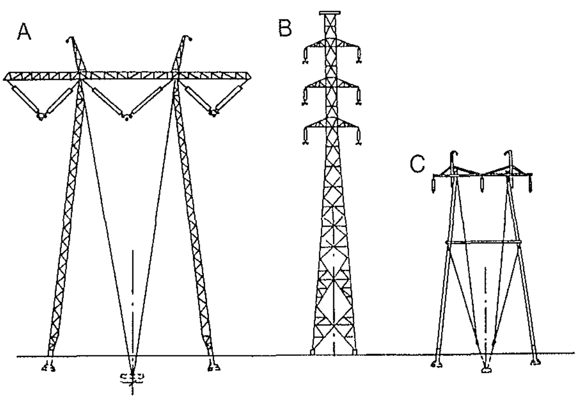

Figure 1. Typical tower types for high-voltage power lines in Finland. (A = a 400 kV tower of portal type, made of steel; B = a 110 kV tower of tannenbaum type, which is common in more densely populated areas; C = a wooden 110 kV tower of portal type) (57).

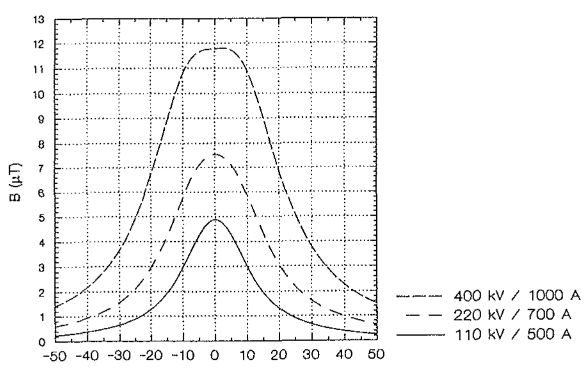

Figure 2. Magnetic flux density by distance from the closest power line as calculated for 110 kV, 220 kV, and 400 kV power lines of portal type, at the height of 1 m above the ground (57).

Power-line fields

In Finland, as in the rest of Europe, the frequency of electric power is 50 Hz as opposed to 60 Hz in North America. Electricity is transmitted from the site of its generation at high voltages for the purpose of transmission efficiency. The voltages of transmission lines in Finland are 400 and 220 kV; the power lines of 110 kV can have characteristics of both transmission and distribution lines. Therefore, the changes in load of the 110-kV lines either depend on the large-scale power balance of the grid or they follow a regular time-related pattern. After transmission, the voltage is transformed at substations to the 10—70 kV in distribution lines and, finally, by local transformers into the 400 V three-phase system. The phase voltage between one of the three phase conductors and the neutral conductor is nowadays 230 V. Some typical types of towers for high-voltage power lines are shown in figure 1.

The power lines generate both electric and magnetic fields, which are usually analyzed separately. High-voltage lines are generally electrically well balanced, and phase currents are sinusoidal and therefore lead, according to Deno & Carpenter (2), to a close correspondence between the calculated and measured fields. Figure 2 illustrates the dependence of magnetic flux density on the distance from the nearest power line for three types of lines: 110 kV, 220 kV and 400 kV.

The magnetic field of a power line may or may not dominate the background magnetic field — originating from electric appliances and installations in the building. Useful factors for assessing the magnetic field of a line have been summarized to be (2): (i) the line current, (ii) the distance of the residence from the power line, (iii) the line configuration, and (iv) the unbalanced current through a ground path.

Residential and occupational magnetic fields

Magnetic fields at households and occupational settings are usually made up of a background field from household electric appliances and nearby cables with unbalanced currents. The average background magnetic field level at Finnish homes without an external magnetic field source (such as a power line or transformer) has been estimated typically not to exceed 0.1 µT (3). Magnetic fields from electric appliances are usually higher than the background fields, and they are highly localized, decreasing roughly in an inverse proportional manner to the square of the distance between the observation point and the source of the magnetic fields. The electric appliances can however, draw considerable current and be close to people, and therefore the magnetic fields associated with their use can be a significant source of exposure. Some examples of household fields are summarized in appendix 1 (3).

Occupational exposures are of the same type as household exposures, but measurements indicate that occupational exposures tend to be somewhat higher. Several publications describe the magnetic field exposures in North America (4—7), whereas some other publications are perhaps more likely to pertain — because of differences in voltage and work procedures — to the occupational environments in Finland (8—11). The majority of the magnetic field recordings have, however, been solely published in national journals (in Finnish) (12—15) or have remained unpublished. Other reports have focused more on the aspect of reducing field levels (16—18).

In a very recent Swedish study (11), the 50th percentile for the workday average of magnetic field exposure was 0.17 μT, and the 75th percentile was 0.27 μT. For median values, the 50th percentile was 0.11 μT and the 75th percentile was 0.16 μT. The maximum values were within the range of 0.15—1088 μT, with a median of 4.98 μT. There were some occupations that had a higher magnetic field level than other occupations. Among the highly exposed groups (with either high workday mean levels or high maximum values) were welders, forestry workers, metal workers, railroad conductors and traffic controllers, postal workers, installation, machine and electric power electricians, chemical engineers and technicians, sales personnel, crane and hoist operators, machine assemblers and machine and motor repair workers, electrical and electronics engineers and technicians, and plumbers and pipe fitters (11).

Methods for exposure assessment

In the epidemiologic studies on ELF magnetic fields and cancer, the following set of exposure assessment methods have been used: (i) distance from electricity power lines and other transmission facilities, (ii) wiring configuration codes for nearby power lines, (iii) calculated magnetic fields of nearby power lines, (iv) measured magnetic fields at home or in the occupational setting, (v) use of household electric appliances, and (vi) job titles.

Each of these approaches has, however, advantages and weaknesses. The measurement of magnetic fields might perhaps appear to be an ideal choice for the purpose of taking fields from a variety of sources into account simultaneously — unless one ignores the facts that the overall magnetic field level varies greatly with time and that the selection of methods is more limited in retrospective studies than in prospective ones. It appears justifiable to assume that the first three methods mentioned may have provided more stable estimates of exposure differentials — if not of absolute exposure levels — over long historical time periods. All the listed exposure assessment methods have been employed in residential studies. The exposure assessment in the majority of occupational studies has however been based on job titles, and only some of the more recently published studies have also employed actual measurements.

Residential studies

Table 1 summarizes the exposure assessment methods used in the published studies on power lines.

Distance. Distance is a very clear measure for the vicinity of power lines but, if magnetic fields are the suspected carcinogenic agent, it disregards the effects of other important factors such as load current and tower type. On the other hand, distance may also correlate with the electric field of the line.

All power-line studies have, in principle, estimated the distance from power lines. The results on cancer risk have sometimes been published for distance per se (19—25), whereas other studies have estimated distance merely as an intermediate step in the process of developing a more specific measure for exposure to magnetic fields of power lines (1, 26, 27). Distance has either been measured from maps (19, 21—23, 28, 29), in nature (1, 26, 27) or both (24, 25).

Wiring configuration codes. The pioneer study by Wertheimer & Leeper (1) was also the first to base its exposure assessment on the use of wiring configuration codes. The purpose was to assess potential historical exposures to magnetic fields. The procedure was simply to visit the chosen address for each subject and to draw a small map of the electrical wires and transformers in the vicinity. The distance was measured from the part of the house closest to the wires with a rollatape. The homes were considered to have "high-current configurations" in three specific instances defined on the basis of the observed wire types and distance. Otherwise the homes were considered to have "low-current configurations."

Later in their adult cancer study (26, 27), Wertheimer & Leeper (1982) distinguished between four categories of wiring configurations with the purpose of facilitating the pair comparisons of their cancer analysis. These categories were (in order of increasing potential for exposure) end-pole situations, ordinary low-current configurations, ordinary high-current configurations, and very high-current configurations. Together the first two categories corresponded to the class of low-current configurations and the last two to the high-current configurations.

Kaune et al (30) showed that selected characteristics of the transmission and distribution wiring in the vicinity of a residence can be used to predict 24-h averaged magnetic field levels, at least in the western part of Wash-

Table 1. Exposure assessment methods used in the published power-line studies.

Study description	Sources of exposure	Voltage	Exposure measure					Cuf-off point or number of categories[a]
			Distance	Code[b]	Magnetic field		Use of appli-ances	
					Mea-sured	Calcu-lated		
Adult cancer studies								
Denver, Colorado, US 1967—1975 (26, 27)	Overhead power lines	All		x				(four)
East Anglia, UK 1971—1983 (19)	Overhead power lines, electricity substations	All	x					15, 35, 50 m
Washington State, US 1981—1984 (32)	Overhead power lines, transformers, other electric constructions < 43 m, electric appliances	All		x	x		x	(four); 0.05, 0.20 μT
Southeast England (21)	Overhead power lines, transformer substations	All	x	x				25, 50, 100 m; (four to five)
Northwest England and Yorkshire, UK 1983—1985 (22)	Overhead power lines, underground cables	240 V—400 kV	x			x		25, 50, 75, 100 m; 0.01, 0.03, 0.10, 0.30 μT
Maastricht, The Netherlands 1961—1987 (23)	Overhead power lines, transformer substations	150 kV	x					100 m
Sweden 1960—1985 (25)	Overhead power lines	220, 400 kV	x			x		50, 100 m; 0.10, 0.20 μT; 1.00, 2.00 μT-years
Childhood cancer studies								
Denver, Colorado, US 1950—1973 (1)	Overhead power lines	All		x				(two)
Rhode Island, US 1964—1978 (100)	Overhead power lines	All		x				(four)
Stockholm, Sweden 1958—1978 (20)	Overhead power lines, electric substations, transformers, electric railroads, electric subways	6—200 kV	x		x			150 m; 0.3 μT
Denver, Colorado, US 1976—1983 (33)	Overhead power lines, underground cables	All		x	x			(two); 0.065, 0.10, 0.20; 0.25 μT
Southeast England (21)	Overhead power lines, transformer substations	All	x	x				25, 50, 100 m
Yorkshire, England 1970—1979 (28)	Overhead power lines	240 V—400 kV	x			x		25, 50, 100 m; 0.01, 0.03, 0.1 μT
Los Angeles County, California, US 1980—1987 (35)	Overhead power lines, electric blankets, water beds, electric clocks, hair dryers, etc	All		x	x		x	(four); 0.068, 0.125 0.268 μT; 0.031, 0.068, 0.125 μT
Mexico City, Mexico (101)	Overhead power lines, transmission towers, transformer substations, transformers, underground cables	High voltage	x					20 m
Sweden 1960—1985 (24)	Overhead power lines	220, 400 kV	x			x		50, 100 m; 0.1, 0.2, 0.3 μT
Denmark 1968—1986 (31)	Overhead power lines, transformer substations, underground cables	50—400 kV				x		0.1, 0.25, 0.40 μT
Finland 1974—1990 (29)	Overhead power lines	110, 220, 400 kV				x		0.20 μT; 0.40 μT-years
Los Angeles County, California, US 1984—1991 (37)	Overhead power lines, other transmission and distribution facilities, underground cables, electric blankets, electric water beds, electric clocks, etc	All		x	x		x	(four); several; highest around 0.3 μT
Washington State, US 1989—1994 (102)	Overhead power lines, other transmission and distribution facilities, underground cables, electric blankets, electric water beds, electric heating, etc	All		x			x	(five)

[a] The latter in parentheses.
[b] A code for wiring configuration in the proximity of each residence.

ington State in the United States. However, the observed correlation between the Wertheimer-Leeper wiring configuration codes and the 24-h averaged residential magnetic field was relatively weak, the correlation coefficient being 0.41. The original Wertheimer-Leeper coding scheme was therefore extended with the aid of an analysis of the relation between the 24-h measurements and the maps of external wiring configurations within 43 m for the same residences. The correlation coefficient for the extended wiring codes and measurements increased to 0.72.

Calculated magnetic fields. The calculation of magnetic fields using historical power-line documents has provided a European alternative to the North American tradition of categorizing wiring configuration codes near homes. There are actually several parallel methods that have been developed independently and employed in epidemiologic studies in the United Kingdom (22, 28), Sweden (24, 25), Denmark (31), and Finland (29). Correlations between the exposure estimates obtained by the various magnetic field calculation methods have not been investigated.

The two English studies, the first one on childhood cancer (28) and the other on adult hematological malignancies (22), based their exposure assessments on the calculation of magnetic fields. The distance from power lines to center points of residences was measured from maps. The aim of the field calculations was to estimate for each address the magnetic fields due to maximum load currents carried by nearby overhead lines during the year of birth (28) or during the five years preceding the diagnosis (22). The magnetic field was calculated for the center of each dwelling at a height of 1 m above the ground.

Magnetic field calculations had some features in common in the Nordic studies. First, all three calculation procedures theoretically took the distance between the subject's residence and nearby power line, historical load current, and tower type into account, and, second, the end product in all three countries was a series of historical estimates for past exposures to annual average magnetic fields. The details of exposure assessment were, however, somewhat different from study to study. In Sweden and Finland, for instance, the exposure source was the overhead transmission power lines (220 and 400 kV or 110, 220 and 400 kV, respectively), whereas in Denmark all overhead power lines, transformer substations, and underground cables (of 50—440 kV) were included. The original data were also documented somewhat differently in each country. For instance, all power documents in Sweden were of paper and included — in the ideal cases — hourly recordings of load current, whereas in Finland the base-line data were for annual average fields and it was stored (from 1983 on) in the data files of a power system simulator. The secondary exposure measures in the Nordic studies were also different with regard to their timing. The Swedish studies explored magnetic fields at the time closest to diagnosis (and some other time points), the Danish study concerned the average between birth and diagnosis, and the Finnish study included the highest annual average and cumulative exposure.

Measured magnetic fields at home. Actual measurements of residential magnetic fields have been employed the most extensively in the North American and Swedish power-line studies. These studies have used somewhat different measurement protocols in which the locations of (spot) measurements have been, for instance, (i) the kitchen, the subject's bedroom, and the family gathering room (32) or (ii) the front door [only this in one study (20)], the child's bedroom, the parents' bedroom, and any additional room occupied by the child for more than an hour per day (33) or (iii) the central room and the rooms closest to and furthest away from the power lines (24, 25).

Measurements have been taken under low power conditions (meaning that many, but perhaps not all, of the electric appliances were turned off to remove in-home field sources) in an effort to isolate the external contribution from the persistent fields produced by outside power lines or under high power conditions as a measure of the combined exposure from outside power lines and wiring in the home.

In addition to spot measurements, magnetic fields have been recorded over 24-h periods with portable dosimeters. The relationship between spot measurements and 24-h measurements was explored by Kaune et al (34), who also developed a subsequent protocol for assessing time-weighted average exposures of children. There are also other examples of secondary exposure measures (eg, means or weighted means) (33, 35) that have been created with the aid of original recordings for magnetic field.

Use of household electric appliances. In an attempt to identify a magnetic field source which would have existed for a long time, most epidemiologic studies have turned their attention to power lines. Use of (household) electric appliances does, however, offer an alternative set of exposure sources, and some studies have included questions on the use of electric blankets, water beds, electric clocks and the like in their questionnaires or interviews (33, 35—37).

Occupational studies

Job titles. During the 1980s, assessments of exposure to magnetic fields from occupational sources were largely based on the researchers' fairly intuitive ideas of what can be considered an "electrical occupation." (See, for example, reference 38.) Cancer risks were evaluated in relation to job titles such as "electrician" or "telephone (power-line) lineman." The workers were thought to have some special source of magnetic fields (electric appliances, electric motors, or power lines) in their vicinity.

Although measurements have indicated that job titles do actually carry information on magnetic field exposure (see the section on residential and occupational magnetic fields on pages 8 and 9), it appears that there is a degree of variation in the actual exposures of workers carrying the same job title. Conscientious measurements have suggested, for instance, that pooling all telephone lineworkers into one category of "telephone lineworkers" may not be totally appropriate (39, 40). Observations of this type have led to the development of detailed job-exposure matrices. In the telephone lineworker study (39, 40), for instance, the secondary exposure assessment culminated in a lifetime exposure score that was based on grouping jobs by similarity of work tasks and exposure environments, on measuring personal exposures to magnetic fields in samples of subjects, and on evaluating a variety of person-level exposure indices (eg, central tendency, peak exposure, maximum exposure, and exposure variability).

Measured magnetic fields in the occupational setting. Later studies have generally developed job-exposure matrices that link job titles to the estimated exposure to magnetic field level and examined the relationships between different summary measures of magnetic field exposure. In a recent Swedish study by Floderus et al (11, 41), for instance, the occupational exposure was assessed from the work history of the questionnaire and from personal monitoring with a dosimeter; complementary information on the magnetic field exposure and on confounders was obtained in interviews at workplaces. The selection of occupations in this population-based study was perhaps wider than in any of the earlier studies, including a total of 1015 measurements taken in different workplaces during a four-year period (41). In statistical analyses, different exposure indices, such as mean, median, quartiles, standard deviation, and time spent above 0.20 µT, were attempted. Other evaluations of exposure indices have also been made (42, 43).

In a large Canadian study by Thériault et al (44), each participant's cumulative exposure to magnetic fields was estimated using personal dosimetry measurements of a sample of 2066 workers (1% of all). Estimates were made of past exposure according to the knowledge of present loading, work practices, and usage. Cumulative exposures were calculated for the duration of employment for the three periods of five calendar years immediately preceding the diagnosis, 20 years preceding the diagnosis, and 20 years or more preceding the diagnosis. The participants were divided into four groups by exposure to magnetic fields, the group boundaries at the 50th, 75th, and 90th percentiles of each exposure index being obtained for all the participants in the study. Odds ratios were estimated for each group and for the top three groups combined (≥ median), relative to the lowest (<median). Some further studies (45—48), too, have linked individual work histories to magnetic field measurements.

Suggested carcinogenic mechanisms

There are now several scientific publications (49—54) and governmental reports (eg, 55—57) which present comprehensive reviews on the issue of the biological and possibly carcinogenic effects of magnetic fields. Overall, some molecular biological and cellular changes have been reported to be initiated by exposure to ELF electromagnetic fields (eg, 50, 51), but the reproducibility of these experiments, as well as their practical relevance to carcinogenesis, have remained controversial. Today, there is no known mechanism by which ELF magnetic fields could cause cancer in general or leukemia in particular.

However, the primary site of interaction — if any — is thought to be at the level of the plasma membrane (58). It also appears that ELF electromagnetic fields are not directly genotoxic (ie, they do not induce cancer) (52), but rather they could act in the later stages of cancer promotion or progression (53). Some more recent experiments have, in addition, introduced the possibility of cocarcinogenesis of ELF electromagnetic fields with certain chemical carcinogens (eg, 7,12-dimethylbenzanthracene) (59).

As to more specific carcinogenic mechanisms, it has been suggested (58) that the activity of adenosine deaminase, a membranal enzyme, might be controlled by lipid protein interactions that have been induced by ELF magnetic fields and thereafter modulate the vertical motion of adenosine deaminase within the lipid core of the plasma membrane. Anomalous adenosine deaminase activity as such had earlier been reported for malignancies such as chronic lymphocytic leukemia (60) and chick embryo fibroblasts transformed by Rous sarcoma virus (61).

Of the other suggested carcinogenic mechanisms of electromagnetic fields, the melatonin hypothesis (62, 63) has evoked an increasing amount of attention. According to this hypothesis, electric power might increase the risk of cancer because electromagnetic fields can reduce melatonin and because reduced melatonin can, in turn, increase the risk of certain cancers. Although the evidence has been assessed to be strongest for breast cancer, the hypothesis might, according to Stevens, pertain also in the case of leukemia.

General epidemiology of leukemia

The term leukemia covers a group of malignant diseases of the blood-forming tissues, which constitute less than 5% of all cancers. Despite extensive studies relatively little is known regarding the causation of leukemia.

Classification

Leukemias are classified according to the origin of leukemic cells, the common types being lymphatic or myeloid in origin. The rarer varieties are monocytic, basophilic, eosinophilic, plasma cell, erythroleukemia, and hairy cell leukemias. Most cell types can be further divided into two major groups — acute and chronic — depending on the degree of cellular differentiation. Many epidemiologic studies have, consequently, subclassified leukemias into acute myeloid (AML), chronic myeloid (CML), acute lymphatic (ALL), and chronic lymphatic (CLL) leukemia. The inclusion of data on histopathology, cytogenetics, immunophenotype, and molecular genetics have recently been suggested to enhance risk factor identification and thus lead to a better understanding of the pathogenesis of leukemia (64).

Descriptive epidemiology

The mean annual number of new leukemia cases was 407 in Finland in 1980—1990 (table 2) (according to the Finnish Cancer Registry data). Of these cases, 362 (87%) were diagnosed in adults and 45 (13%) in children. Twenty-nine percent were AML, 15% ALL, 11% CML, and 31% CLL. The majority of cases in children belonged to the ALL category.

The risk of leukemia is higher among men than among women. The male-female ratio of the incidence rates was 1.5 for the whole of Finland in 1980—1990 when based on the age-adjusted incidence rates of $8.9 \cdot 10^{-5}$ for men and $6.0 \cdot 10^{-5}$ for women (according to data from the Finnish Cancer Registry). The respective mortality rates were $5.9 \cdot 10^{-5}$ for men and $3.7 \cdot 10^{-5}$ for women while the mean annual number of deaths due to leukemia was 326 (according to data from the Finnish Cancer Registry).

The incidence of leukemia varies widely by age, from 1 to 2 per 100 000 in young adulthood to 25 or more per 100 000 at ages over 70 years. However, a distinct childhood peak exists between 2 and 4 years in industrialized countries, whereas it is less pronounced in the former Eastern European countries and absent in the developing countries. A childhood peak may not have existed at all prior to the 1920s (65). While the cause of the peak is debatable, it is conceivable that it reflects exposures in utero or in very early infancy (65).

Leukemia incidence, as reflected in mortality data, increased dramatically from 1900 to the 1940s, at least in North America. While much of this rise was undoubtedly due to improved diagnostics and more accurate death registration, some at least can be presumed to reflect true increased occurrence (65). In the last 10 years, the incidence of leukemia in Finland has decreased by one-fifth for both genders. Parallel tendencies have been reported in other countries, too (66). The decrease was somewhat slower for AML than for CLL or other types of leukemia.

Table 2. Mean annual number of new leukemia cases in 1980—1990 in Finland, by subtype.

Subtype	Number	Percentage
Acute myeloid leukemia	120	29
Chronic myeloid leukemia	46	11
Acute lymphatic leukemia	63	15
Chronic lymphatic leukemia	128	31
Monocytic leukemia	8	2
Myeloid leukemia, unspecified	8	2
Lymphatic leukemia, unspecified	4	1
Other leukemia, specified	9	2
Acute leukemia, unspecified	11	3
Leukemia, unspecified	10	3
Total	407	99

Geographic differences for leukemia occurrence rarely exceed twofold for countries with comparable reliability and accuracy in the reporting of mortality or incidence (65). The most striking difference involves CLL, which has very low rates among Asians, but differences have also been identified for geographic, racial-ethnic, age, and trend patterns of other leukemia subtypes (66). In many reports, the leukemia rates have been somewhat higher for urban than for rural settings (65), whereas no such difference or a geographic pattern has been apparent in Finland (67).

In a recent Finnish study, the social class variation in leukemia incidence was rather small (68), but, nevertheless, the leukemia incidence was higher in the higher socioeconomic classes. This association has also been observed in other studies (65).

Etiologic factors

Overall, the rather modest geographic variation in leukemia incidence suggests that environmental factors are relatively weak or ubiquitous. Some cases of leukemia are related to inherited chromosome abnormalities. Exogenous ionizing radiation is an important cause. It also appears likely that long-term smoking may contribute to the pathogenesis of leukemia, AML in particular (69).

Hereditary factors. Various lines of evidence indicate the influence of genetic factors in human leukemia epidemiology. The variation between ethnic groups, such as the rarity among persons of Oriental origin, suggests that ethnic factors may be involved (65). Familial leukemia cases may have occurred, but the evidence remains somewhat inconsistent (70). There are associations between leukemia occurrence and various genetic markers, for example, the Philadelphia chromosome (ie, partial deletion of chromosome 22) is observed in about 90% of patients with CML (65). Some inborn or acquired chromosome anomalies such as Down's syndrome, Bloom's syndrome and Fanconi's aplastic anemia clearly predispose to leukemia (71). In one study, the proportion of childhood leukemias attributable to inherited mutations was estimated to be 2.6% (72).

Ionizing radiation. Ionizing radiation is generally considered an important etiologic factor for leukemia and could, according to Higginson (73), account for up to 10% of cases in some communities. Evidence comes from several sources, including increases in the risk among early radiologists and in men subject to X-ray therapy for ankylosing spondylitis. Cases have been reported after occupational exposure and modest increases in risk for children having been exposed to prenatal diagnostic X rays (73). One Finnish study observed a twofold increase (nonsignificant) in the risk of leukemia among children exposed to pelvic X rays prenatally (74). Increases have also been observed in Japanese populations surviving the atomic bomb explosions in Hiroshima and Nagasaki (75) and in those exposed to atom bomb testing (76).

The possibility that ambient radiation around nuclear power plants may cause leukemia and other cancer is a matter of great concern. Gardner et al (77, 78) reported that the relative risks for leukemia and non-Hodgkin's lymphoma were higher for children born near the Sellafield nuclear plant in the United Kingdom and for children whose fathers were employed at the plant. These findings have, for lack of additional evidence, remained controversial (79). A recent study on the relation between exposure caused by the Chernobyl accident fallout and incidence of childhood leukemia in Finland excluded any important increase in risk (80). Another recent study on cancer incidence among Finnish airline cabin attendants (with exposure to presumed cosmic radiation) observed an (nonsignificant) increase in the risk of leukemia [2 cases observed, standardized incidence ratio (SIR) 3.57, 95% confidence interval (CI) 0.43—12.9] (81).

Chemicals. Chemical-related cases of leukemia have been estimated to be less than 1% of the total (73). Although benzene is considered carcinogenic to humans [in group 1 of the IARC classification of carcinogens (82)], the hazard level is not known. Benzene-related leukemias tend to be of the AML type, but some cases of CML and CLL have been reported. A recent ecological study addressed the possible long-term effects of exposures to low concentrations of benzene; the findings were not supportive of an association between gasoline consumption and reported leukemia incidence and mortality rates (83). Other chemicals that have been suspected to be leukemogenic include styrene (84), chlorophenols (85) and hydrocarbons (86). One recent study on the mutagenicity of drinking water and leukemia observed no association (87).

Cancer treatment. The net effect of cancer treatment on the occurrence of primary leukemia, for example, was evaluated in a Finnish study on multiple cancer with the use of cancer registry data (88). Overall, there was an increased risk of leukemia (other than CLL) among the cancer patients (men: 45 cases observed, SIR 1.41, $P<0.05$; women: 88 cases observed, SIR 2.16, $P<0.001$), particularly so among the patients with cancers of the breast, endometrium, and thyroid gland. Other types of primary cancer associated with an increased risk of secondary leukemia include Hodgkin's disease (89) and small-cell lung cancer (90). These observations of risk increases in secondary leukemia can be interpreted as an effect of irradiation treatment and the administration of chemotherapeutic drugs, the latter being more significant in the case of leukemia (89, 91, 92). The chemotherapeutic drugs in question include cyclophosphamide (IARC group 1) (82), melphalan (IARC group 1), and MOPP (mechlorethamine-vincristine-procarbazine-prednisone), and other combined chemotherapies including alkylating agents (IARC group 1).

Smoking. Leukemia has traditionally not been recognized as a smoking-related cancer. However, Austin & Cole (93) published a review suggesting that there was some support for a causal relation between smoking and leukemia, and therefore stimulated more epidemiologic research on the topic. The new studies were reviewed, for example, by Siegel (94), who concluded that smoking appears to cause AML. He calculated that the population attributable risk was 22%, which would make smoking the leading known cause of leukemia. Some other independent reviews (95, 96) have published coinciding conclusions.

Infectious agents. After viral leukemia in rodents and other animals was demonstrated, there has been considerable interest in the role of viruses in human leukemia (97). For instance, a human retrovirus, HTLV (human T-cell leukemia virus), has been shown to cause adult T-cell leukemia and lymphoma in Japan. In addition, the observation that leukemia often occurs in spatial or temporal clusters has enhanced investigations of the possibility of a viral etiology for leukemia. For instance, one explanation offered for the reported clusters of leukemia surrounding nuclear installations has been the possibility that increased risks were due to an influx of new persons and new viruses into previously isolated communities (64). Viruses have also been proposed to explain the associations between power lines and childhood cancer (98). In one study, there was a suggestion that children with leukemia had moved more often during the first few years of life than other children had (99).

Residential magnetic fields and childhood cancer

It was the epidemiologic study on power lines and childhood cancer by Wertheimer & Leeper (1) in 1979 that was the actual beginning of research on magnetic fields and carcinogenesis. The results of the first study suggested a threefold increase in the overall cancer risk among Denver children living near power lines. Many of the controversial features of this first study have later been shared by other residential and occupational studies. These features include the difficulties in exposure characterization, the problem of small numbers and the lack of a specific outcome event. Despite some deficiencies in design, confounding or other biases have been suggested but not demonstrated to explain the observed associations.

Table 3 presents the results of the 13 epidemiologic studies (1, 20, 21, 24, 28, 29, 31, 33, 35, 37, 100—102) that have so far been published on the relation between power lines and childhood cancer; there has been one additional study on the use of electric appliances (36). Most of the childhood cancer studies have found weak increases in the risk of childhood cancer with exposure. The implication of the small numbers of exposed cases in each individual study is that these investigations have to be considered together for interpretation. The magnitude of risk can be illustrated, for example, with medians and ranges of what can be considered to be the most reliable risk estimates (based also on largest numbers), which are 1.5 (from 0.99 to 2.2) for total childhood cancer, 1.6 (from 0.3 to 3.8) for leukemia, and 1.5 (from 0.9 to 3.7) for nervous system tumors. The pooled analysis (103) of the three Nordic studies (24, 29, 31) supported more clearly the hypothesis of a risk increase in leukemia than a risk increase in nervous system tumors, and the evidence has been assessed to be the most prominent for leukemia in children (104). Two more recent childhood cancer studies, both solely on brain tumors, were published in 1996. The results of the Los Angeles study (37) were consistent with the hypothesis of elevated risk only in relation to exceptionally high residential exposures of ≥ 0.3 µT, whereas the Seattle study did not observe any risk increases for magnetic fields during the three-year period immediately before the diagnosis (102). These studies thus continue to maintain the controversy surrounding the hypothesized association between magnetic fields and cancer.

Occupational magnetic fields and adult leukemia

In 1982, in a letter to the *New England Journal of Medicine*, Milham (38) reported a relationship between electrical occupation and leukemia mortality in Washington State in the United States in 1950—1979. The proportionate mortality ratio (PMR) for all "electrical occupations" was 1.37 for all leukemia ($P<0.01$) and 1.63 for acute leukemia ($P<0.01$). An elevation was apparent for 10 out of 11 occupations with presumed exposure to electromagnetic fields. Stronger associations were found for some specific groups of electrical workers, including

Table 3. Studies on childhood cancer and residence near power lines. (RR = relative risk, 95% CI = 95% confidence interval)

Study description	Exposure measure	Leukemia			Nervous system tumors			All cancers		
		Exposed cases	RR	95% CI	Exposed cases	RR	95% CI	Exposed cases	RR	95% CI
Denver, Colorado, US, 1950—1973 (1)	Wiring codes	63	3.0[a]	1.8—5.0[a]	30	2.4[a]	1.2—5.0[a]	129	2.2[a]	1.6—3.1[a]
Rhode Island, US, 1964—1978 (100)	Wiring codes	103[a]	1.1[a]	0.73—1.6[a]	.	.	.	.	.	.
Stockholm, Sweden, 1958—1973 (20)	Distance (< 150 m)	5	1.1[a]	0.29—4.1[a]	9	3.9[a]	0.85—19[a]	32	2.1[a]	1.1—4.1[a]
	Measured magnetic field (≥ 0.3 µT)	4	0.3[a]	0.10—1.1[a]	13	3.7[a]	1.1—13[a]	34	2.1[a]	1.1—4.0[a]
Denver, Colorado, US, 1976—1983 (33)	Wiring codes	27	1.5	0.90—2.6	20	2.0	1.1—3.7	89	1.5	1.0—2.3
	Measured magnetic field (≥ 0.2 µT)	5	1.9	0.67—5.6	2	1.0	0.22—4.8	13	1.4	0.63—2.9
Southeast England, (21)	Distance (< 50 m)	14	1.5	0.7—3.4	.	.	.	.	.	.
Yorkshire, England, 1970—1979 (28)	Distance (≤ 150 m)	.	.	.	.	.	.	20	0.99[a]	0.56—1.8
Los Angeles County, California, US, 1980—1987 (35)	Wiring codes	42	2.2	1.1—4.3	.	.	.	.	.	.
	Measured magnetic field (≥ 0.27 µT)	20	1.5	0.66—3.3	.	.	.	.	.	.
Mexico City, Mexico (101)	Distance	40	2.6	1.3—5.4	.	.	.	.	.	.
Sweden 1960—1985, (24)	Calculated magnetic field (≥ 0.3 µT)	7	3.8	1.4—9.3	2	1.0	0.2—3.9	10	1.3	0.6—2.7
	Distance (≤ 50 m)	6	2.9	1.0—7.3	1	0.5	0.0—2.8	9	1.0	0.5—2.2
Denmark 1968—1986, (31)	Calculated magnetic field (≥ 0.25 µT)	3	1.5	0.3—6.7	2	1.0	0.2—5.0	6	1.5	0.6—4.1
	Calculated magnetic field (≥ 0.40 µT)	3	6.0	0.8—44	2	6.0	0.7—44	6	5.6	1.6—19
Finland 1974—1990, (29)	Calculated magnetic field (≥ 0.20 µT)	3	1.6	0.32—4.5	5	2.3	0.75—5.4	11	1.5	0.74—2.7
	Calculated cumulative exposure (≥ 0.40 µT-years)	3	1.2	0.26—3.6	7	2.3	0.94—4.8	15	1.4	0.77—2.3
Los Angeles County, California, US, 1984—1991 (37)	Wiring codes	.	.	.	31	1.2	0.6—2.2	.	.	.
	Measured magnetic fields (≥ 0.30 µT)	.	.	.	12	1.7	0.6—5.0	.	.	.
Washington State, US, 1984—1990 (102)	Wiring codes	.	.	.	23	0.9	0.5—1.5	.	.	.

[a] Numbers of exposed, unmatched odds ratios and 95% confidence intervals calculated on the basis of published data.

power station operators, aluminum workers, and television and radio repairmen. Little or no increased risk was noted for welders, flame cutters, and electrical engineers.

During the next 10 years, a series of PMR reports on leukemia risk among electrical workers was published (27, 105—109), whereas the more recent studies have applied either cohort (47, 110—113) or case-referent design (41, 44, 114—116). Some of the more recent studies have incorporated extensive magnetic field measurements into their exposure assessment (41, 44, 47, 113, 116). The studies on total leukemia in relation to all electrical occupations, or in relation to extensive field measurements, are presented in table 4, but there are also studies that have been limited to a specific occupation [eg, telephone linemen (40)] or branch of industry [eg, railways or hydroelectric power plant workers (117—119)].

Tynes et al have conducted three studies (111, 117, 119) on occupational magnetic fields and cancer in Norway. The first of them (111) evaluated the risk of cancer in a cohort of 37 945 male Norwegian electrical workers for whom information on job description was first collected from the 1960 census data and further linked to 1970 census data. The SIR for leukemia for electrical workers with 10 or more economically active years was 1.41 (74 cases observed, 95% CI 1.10—1.76). The figures for AML, CLL and CML were 1.56 (29 cases observed, 95% CI 1.06—2.26), 1.97 (15 cases observed, 95% CI 1.10—3.26) and 1.26 (20 cases observed, 95% CI 0.77—1.94), respectively. The second study (119) investigated cancer risk in a cohort of 5088 men who had worked for at least one year between 1920 and 1991 for a hydroelectric power company; the relative risk of leukemia in this study corresponded to that expected on the basis of national rates. The nested case-referent study of railway workers (117) showed that men employed on electric railways had an odds ratio for leukemia of 0.7 when compared with men employed on nonelectric railways.

Guénel et al (112) studied cancer incidence in 1970—1987 in a cohort of 2.8 million Danes aged 20—64 years in 1970. Each person was classified by his or her industry and occupation in 1970; each industry-occupation group was coded for potential exposure to magnetic fields according to information from the literature and few field measurements. Some 154 000 men were considered intermittently exposed and 18 000 were continuously exposed. The numbers for the women were 79 000 and

Table 4. Leukemia risk by occupational exposure to electromagnetic fields. (RR = relative risk, 95% CI = 95% confidence interval, PMR = proportionate mortality ratio, PIR = proportionate incidence ratio, PRR = proportional registration rate, Q3 = quartile with the second highest exposure, Q4 = quartile with the highest exposure, NS = not significant)

Study description	Study design	Exposed cases	RR	95% CI or P-value[a]
Studies with electrical occupations				
Washington State, US, 1950—1979 (38)	PMR	136	1.37	(< 0.01)
Los Angeles County, California, US, 1972—1979 (105)	PIR	35	1.29	(> 0.05)
Southeast England, 1961—1979 (106)	PRR	113	1.17	(< 0.05)
England and Wales, 1970—1972 (107)	PMR	85	0.98	(NS)
Wisconsin, US, 1963—1978 (108)	PMR	81	1.03	(NS)
US, 1950—1979 (27)	PMR	171	1.16	(≤ 0.10)
New Zealand, 1980—1984 (114)	Case-referent (incidence, cancer referents)	21	1.62	1.04—2.52
Finland, 1971—1980 (110)	Cohort (incidence)	94 possible and 10 probable	1.42 1.85	1.1—1.8 1.0—3.5
16 US, 1985—1986 (115)	Case-referent (mortality)	38 for < 65 years and 38 for ≥ 65 years	1.3 0.8	0.9—1.7 0.6—1.1
14 US, 1979—1985 (109)	PMR	183	1.19	1.02—1.37
Norway, 1961—1985 (111)	Cohort (incidence)	74	1.41	1.10—1.76
Denmark, 1970—1987 (112)	Cohort (incidence)	39	1.64	1.20—2.24
Studies with extensive field measurements				
Southern California, US, 1960—1988 (113)	Cohort (mortality)	39	1.09	0.51—2.29
Mid-Sweden, 1983—1987 (41)	Case-referent (incidence)	61 for Q3 and 80 for Q4	1.2 1.6	0.8—1.9 1.1—2.4
Canada and France, 1970—1989 (44)	Case-referent (incidence)	70	1.54	0.90—2.63
Los Angeles County, California, US, 1972—1990 (116)	Case-referent (incidence, cancer referents)	121	1.3	1.1—1.6
US (five electric utility companies), 1950—1986 (47)	Cohort (mortality)	82 for < 5 years 54 for 5—19 years and 28 for ≥ 20 years	1.00 1.31 1.00	. 0.87—1.97 0.60—1.65

[a] The latter in parentheses.

4000, respectively. Intermittent exposure was not associated with an increased risk of leukemia. However, men with continuous exposure had an excess risk of leukemia (39 cases observed, SIR 1.64, 95% CI 1.20—2.24) with equal contributions from acute and other leukemias. For the continuously exposed men, the risk for leukemia was mainly found for electricians in installation works and iron foundry workers. No excess risks of leukemia were observed in women in association with magnetic field exposure.

Sahl et al (113) evaluated leukemia mortality in 1960—1988 in a cohort of 36 221 electric utility workers using cohort analyses and a nested case-referent design. Exposure information was derived from company job history information and a total of 776 days of magnetic field measurements. In job title analyses, the age-specific cancer rates for electric and reference workers were similar; an odds ratio (OR) of 1.09 (13 observed cases, 95% CI 0.51—2.29) was observed for leukemia among electrical workers in comparison with other field and craft occupations and office and technical support staff. The OR values for the magnetic field exposure indices were all close to or less than 1.0 when they were based on scores for the mean, median, 99th percentile, and fractions exceeding 1 μT and 5 μT.

A case-referent study by Matanoski et al (40) examined the potential associations between telephone linework and mortality from all types of leukemia except CLL in a retired occupational population in 1975—1980. Exposure was defined both by job title and by a lifetime exposure score. The workers with exposure scores above the median for the population showed a 2.5 times higher risk of leukemia than those with scores below the median (95% CI 0.7—8.6). Moreover, there was a suggestion of an increase in risk with exposure duration (intermittent peak exposures) and long latency period (10 or more years); workers with peak exposure scores above the median had OR values of 2.4 (95% CI 0.7—9.0) and 6.6 (95% CI 0.7—58) for latency periods of 10 and 15 years, respectively.

Floderus et al (41) studied occupational exposure to low-frequency electromagnetic fields in 250 leukemia patients diagnosed in 1983—1987 and compared with a reference group of 1121 randomly selected men. The exposure assessment was based on measurements from 1015 different workplaces (11). On the basis of the job held longest during the 10-year period before the diagnosis, an association was observed between the mean of the daily average magnetic field and CLL. The risk increased with increasing level of exposure. The OR values for three consecutive levels of exposure were 1.1 (95% CI 0.5—2.3), 2.2 (95% CI 1.1—4.3), and 3.0 (95% CI 1.6—5.8), respectively. No association was observed for AML. Different exposure indices were tested. Tasks with frequent or large variations between high and low field densities were more common for the CLL subjects. Confounding by place of residence, smoking, benzene, ionizing radiation, pesticides, and solvents was evaluated, and these factors did not seem to have a decisive influence on the associations. For CLL, there were indications of an excess number of low-exposure subjects among the nonrespondents, and, to some extent, this excess may have enhanced but not caused the risk estimates obtained.

Another Swedish study by Floderus et al (118) reanalyzed the 1961—1979 cancer incidence data (previously showing no increase in the risk for leukemia among railway workers) dividing the follow-up into two 10-year periods. For the first decade, the locomotive engineers and conductors combined had relative risks (RR) of 1.9 (95% CI 0.9—4.0), 1.4 (95% CI 0.4—4.3), and 1.0 (95% CI 0.5—1.9) for CLL, AML, and lymphoma, respectively, when they were compared with the general population. The latter decade showed no increases.

To determine whether occupational exposure to magnetic fields of 50—60 Hz was associated with cancer among electric utility workers, Thériault et al (44) used a case-referent design nested within three cohorts of a total of 223 292 workers at electric utilities; 4 151 new cases of cancer occurred during the follow-up in 1970—1989. Exposure assessment was based both on magnetic field measurements for a sample of workers and on occupational histories. Workers who had more than the median cumulative exposure to magnetic fields (3.1 μT-years) had a higher risk for acute nonlymphoid leukemia (33 exposed cases, OR 2.41, 95% CI 1.07—5.44). The same observation held for AML (26 exposed cases, OR 3.15, 95% CI 1.20—8.27). There was also an elevated risk for mean exposure above 0.2 μT (acute nonlymphoid leukemia, 26 exposed cases, OR 2.36, 95% CI 1.00—5.58; AML, 20 exposed cases, OR 2.25, 95% CI 0.79—6.46). However, there were no clear dose-response trends with increasing exposure and no consistency among the three utilities.

London et al (116) performed a register-based case-referent study among men who were between the ages of 20 and 64 years, had known occupation, and had been diagnosed with cancer in Los Angeles County in the United States between 1972 and 1990. The referents were men with cancers other than those of the central nervous system or leukemia. Magnetic field measurements on workers in each electrical occupation and in a random sample of occupations presumed to be nonelectrical were used to estimate the magnetic field exposures for each occupation. For the men in electrical occupations, 121 leukemias were diagnosed. With the exception of electrical engineers, magnetic field exposures were higher for the workers in electrical occupations than for those in nonelectrical occupations. A weak positive trend in leukemia risk was observed across the average occupational magnetic field exposure (the OR per 1 μT increase being 1.2, 95% CI 1.0—1.5). A slightly stronger association was observed for CML, although only 28 cases occurred among the electrical workers (the OR per 1 μT increase being 1.6, 95% CI 1.2—2.0).

The results of Savitz & Loomis (47) did not support an association between occupational magnetic field exposure and leukemia. They conducted a historical cohort mortality study of 138 905 men employed at five large electric power companies in the United States between 1950 and 1986 with at least six months of work experience. Exposure was estimated by linking individual work histories to data from 2842 workshift magnetic field measurements. Mortality follow-up identified 20 733 deaths based on 2.66 million person-years of experience. Total mortality and cancer mortality rose slightly with increasing magnetic field exposure. Leukemia mortality, however, was not associated with indices of magnetic field exposure except for work as an electrician.

In summary, several studies have suggested that work in electrical occupations is associated with an increased risk of leukemia; some of the most recent studies with extensive magnetic field measurements have supported the earlier observations of risk increase, whereas others have not. The greatest limitation of these occupational studies is perhaps that power-frequency magnetic field exposures vary substantially between persons, occupations, and industries. Other limitations include failures to consider potential confounders or biases. The published investigations may not be representative of all studies because the PMR studies showing risk increases may well have been published easier than those showing no such increases.

Residential magnetic fields and adult leukemia

Before this study, there were only seven published reports on power lines and hematological malignancies in adults (19, 21—23, 25, 27, 32) (table 5). In one of them, the number of study subjects was so small that no leukemias occurred during the follow-up for cancer (23). One other study investigated the risk of leukemia with regard to the use of electric blankets (120) and two others concentrated on the risk of leukemia among radio amateurs (121, 122). Two studies applied a cohort design (19, 32), whereas all the others were case-referent studies. Three studies included, in principle, all cancer subtypes (19, 27, 32), contrary to the others, which were more specific in their study hypotheses.

The Colorado study

In the study of Wertheimer & Leeper (26, 27), a total of 1179 cases of adult cancer was assembled from the

Table 5. Studies on adult leukemia and residence near power lines. Numbers in parentheses denote 95% confidence intervals and numbers in double parentheses are the numbers of exposed cases. (SMR = standardized mortality ratio, OR = odds ratio)

Study description	Study design	Exposure measure	Risk estimate	Outcome of interest				
				Acute myeloid leukemia	Chronic myeloid leukemia	Chronic lymphatic leukemia	Total leukemia	Hematological malignancies[a]
Denver, Colorado, US, 1967—1975 (26, 27)	Case-referent	Wiring code	C ratio	·	·	·	100	133
East Anglia, UK, 1971—1983 (19)[b]	Cohort	Distance (< 50 m)	SMR	·	·	·	1.02 (0.37—2.22) ((6))	1.17 (0.67—1.90) ((10))
Washington State, US, 1981—1984 (32)[c]	Case-referent	Wiring code (high to low; longest residence 3—10 years before diagnosis)	OR	1.15 (0.62—2.2) ((26))	·	·	·	·
		Wiring code (high to low; residence closest to diagnosis)	OR	1.48 (0.80—2.7) ((29))	·	·	·	·
Southeast England, UK, (21)[d]	Case-referent	Distance (< 50 m)	OR	0.80 (0.61—1.25) ((26))	0.46 (0.21—1.02) ((7))	1.14 (0.78—1.67) ((40))	1.00 (0.76—1.30) ((97))	·
Northwest England and Yorkshire, 1983—1985 (22)	Case-referent	Distance (< 50 m)	OR	1.22 (0.75—1.98) ((41))	·	·	·	1.29 (0.99—1.68) ((137))
		Calculated magnetic field (≥ 0.30 μT)	OR	no referents	·	·	·	1.87 (0.79—4.42) ((15))
Sweden, 1960—1985 (25)	Case-referent	Distance (< 50 m)	OR	1.1 (0.4—2.8) ((5))	2.4 (1.0—5.1) ((8))	1.0 (0.5—2.1) ((8))	1.2 (0.7—2.0) ((24))	·
		Calculated magnetic field (≥ 2.0 μT-years)	OR	2.3 (1.0—4.6) ((9))	2.1 (0.9—4.7) ((10))	1.3 (0.6—2.6) ((10))	1.5 (1.0—2.4) ((29))	·

[a] The risk estimates for "hematological malignancies" denote slightly differing cancer groups in individual studies: Wertheimer & Leeper and McDowall included leukemia, Hodgkin's disease, non-Hodgkin's lymphoma and multiple myeloma, whereas Youngson et al included leukemia and non-Hodgkin's lymphoma only.
[b] SMR and 95% confidence intervals calculated according to the published data.
[c] Acute nonlymphatic leukemia, calculated according to the published data.
[d] Risk estimates for distance to nearest substation.

records covering Denver and its suburbs and two smaller towns near Denver in the Colorado Death Certificate and Cancer Registry. The decedents had been diagnosed either in 1977 (in Denver and its suburbs) or in 1967—1975 (in the other two towns); the cases chosen from cancer survivors had to be without any known recurrence of cancer by 1979. Neighborhood referents were used for cases in the Denver area; the referents for the small town cases had died from causes other than cancer and were matched for town, gender, age, year of death, years of living in the house, and socioeconomic level. The address at which the case (or referent) had spent most of the period from three to ten years prior to the diagnosis was chosen for the analyses. Each cancer case was compared with its matched referent with the use of wiring configuration codes as a rough index for historical exposure to magnetic fields of power lines. The relative risk for cancer was estimated using C ratios (and not OR values as in the later case-referent studies), which were calculated by dividing the number of matched pairs with a case having higher exposure by the number of pairs with a referent having higher exposure, and multiplying by 100. The selected outcomes of this study were nervous system tumors, leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, cancers of the ovary, uterus, breast, prostate, kidney, bladder, mouth, pancreas, stomach, colon and lung, and other cancers.

The C ratio for all cancers among the adults was 139 ($P<0.0001$) when based on 509 pairs with a more highly exposed case and 367 pairs with a more highly exposed referent. The C ratio exceeded 100 for all four geographic areas; it increased with increasing exposure. The association between magnetic fields and cancer was more impressive for cancers occurring before the age of 55 years, somewhat stronger among the cancer survivors and strongest in the highest socioeconomic class. The association showed no major differences for gender. As to leukemia risk, the C ratio was exactly 100 (23:23). The respective figures were 133 (69:52) for all cancers of the hematopoietic and lymphatic system, 150 (12:8) for Hodgkin's disease, 144 (26:18) for non-Hodgkin's lymphomas, and 267 (8:3) for multiple myeloma — all nonsignificant.

The study subjects were also classified into two categories according to exposure to the (industrial) environment ("the Denver group" and "the non-Denver group"). In general, the non-Denver group showed fairly strong wiring code-cancer associations for cancers of each system except the respiratory system. The Denver group generally showed little or no evidence of such an association. The C ratio for leukemia was 121 (17:14) for the non-Denver group and 67 (6:9) for the Denver group; those for all malignancies of the lymphatic system were 158 (41:26, $P\leq0.1$) and 108 (28:26), correspondingly.

The East Anglia study

McDowall (19) studied the mortality of persons resident in the vicinity of electricity transmission facilities in East Anglia, England, between 1971 and 1983. First, maps of East Anglia were sampled and all electrical installations (electricity substations and overhead power cables) were noted. The 1971 census schedules for all occupied properties in the vicinity of these installations were extracted from records of the Office of Population Censuses and Surveys, and details of each individual resident of the properties were recorded. The National Health Service Central Register then "flagged" these persons and identified the ones who had died or emigrated between the census date and 31 December 1983. Death certificates for the deceased were obtained from the records of the Office of Population Censuses and Surveys, and the mortality of the study population was analyzed with the use of standardized mortality ratios (SMR) in a comparison of East Anglian regional mortality rates and England and Wales national mortality rates. The studied outcome events were overall mortality and mortality from the major groups of malignant, circulatory, and respiratory diseases. Mortality from cancers of the stomach, lung, breast and uterus, leukemias, and other neoplasms of the lymphatic and hematological tissue were considered as separate entities.

Altogether 7631 persons, who had lived within 50 m of a substation or within 30 m of an overhead power cable in 1971, were included in the study cohort; 814 of them had died during the follow-up period of 12 years. The study cohort contributed a total of 91 016 person-years at risk. The overall mortality was lower than expected (409 cases, SMR 87, 95% CI 78—95 for the men; 405 cases, SMR 92, 95% CI 83—101 for the women), and no evidence of major health hazards emerged. The only statistically significant excess mortality was for lung cancer (for all women and for persons living closest to the installations). The SMR values for leukemia were 61 for the men (2 cases observed, 95% CI 7—219) and 154 for the women (4 cases observed, 95% CI 42—394). The SMR values for other neoplasms of the lymphatic and hematological tissues were 94 for the men (4 cases observed, 95% CI 25—238) and 171 for the women (6 cases observed, 95% CI 63—373). The SMR values for leukemia were 143 (1 case), 77 (2 cases) and 120 (3 cases) when analyzed by distance (categories of 0—14, 15—34, and 35—50 m); the comparative figures for malignancies of the other lymphatic tissues were 333 (3 cases), 59 (2 cases), and 147 (5 cases). None of these SMR values reached statistical significance.

The Washington study

Severson et al (32) carried out a population-based case-referent study specifically aimed at testing the hypothesis of a relationship between residential exposure to power frequency magnetic fields and acute nonlymphatic leukemia. A total of 114 incident cases of acute nonlymphatic leukemia were identified from the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center. The leukemias were newly diagnosed between 1981 and 1984 among 20- to 79-year-old people living in the western area of Washington State in the United States. A total of 133 referents was selected from the same area by using a random digit dialing scheme; they were frequency matched to the cases by gender and age. All the study subjects or their next-of-kin were interviewed in person. Exposure measurement was based on the following three methods: (i) electrical wiring configurations, (ii) spot measurements, and (iii) 24-h measurements for a sample of study subjects. Two exposure quantities were calculated from the spot measurements to be used in the cancer analyses: (i) the mean of the three-room measurements and (ii) the mean of the three-room measurements weighted by time spent by the subject in each room.

Neither the measured magnetic fields nor the wiring configuration codes were associated with acute nonlymphatic leukemia. The OR values corresponding to wiring codes (Wertheimer & Leeper's wiring configuration scheme with four exposure categories), by increasing exposure, were 1.00 (42 cases versus 44 referents), 0.60 (21 cases versus 37 referents, 95% CI 0.29—1.22), 0.77 (21 cases versus 23 referents, 95% CI 0.35—1.68) and 0.79 (5 cases versus 6 referents, 95% CI 0.22—2.89) for the longest period of residence 3—10 years before the diagnosis; the respective OR values were 1.00 (42 cases versus 52 referents), 0.81 (26 cases versus 38 referents, 0.41—1.61), 1.36 (24 cases versus 19 referents, 0.62—2.96) and 0.84 (5 cases versus 7 referents, 0.24—2.93) for the residence period closest to the diagnosis. Application of the extended Wertheimer & Leeper wiring classification scheme provided an OR of 0.85 (95% CI 0.40—2.09) for magnetic field exposure of ≥ 0.2 μT in comparison with no such exposure.

The OR for the mean of the magnetic field — under low power conditions — was 1.00 for 0—0.050 μT, 1.16 for 0.051—0.199 μT, and 1.50 for ≥ 0.200 μT; the OR values for the weighted mean of the measured magnetic field under low power configuration were 1.00, 1.17, and 1.03 for the same exposure categories. All the values were statistically nonsignificant.

The southeast England study

A population-based case-referent study on leukemia and residence near electricity transmission equipment was conducted by Coleman et al (21) in southeast England. A total of 771 incident cases of leukemia, identified from the Thames Cancer Registry among residents of four London boroughs during the period 1965—1980, was available for analysis. Two groups of referents were used: (i) 1432 cancer referents with a solid tumor (excluding lymphoma) and eligible exposure data identified from the same registry and individually matched for gender, age, year of diagnosis, and borough and (ii) a group of 231 population referents comprised of a random sample of the general population aged 18 years and over and drawn from the electoral roll for one of the four boroughs. Two kinds of exposure measures were used in the analysis: (i) distance and (ii) exposure indices for distance.

The OR values for leukemia relative to cancer referents were 1.00, 1.33, 2.00, and 2.00 by decreasing distance from an overhead power line (≥100, 50—99, 25—49, and <25 m); the corresponding figures were 1.00, 0.99, 0.89, 1.26 by decreasing distance from substation (same categories). Risk elevations were not observed for the exposure indices or for the population referents. The risk estimates were slightly higher for lymphatic leukemia (OR 1.24, 95% CI 0.90—1.72) than for myeloid leukemia (OR 0.76, 95% CI 0.51—1.11) although the confidence intervals were widely overlapping.

The northwest England and Yorkshire study

The relation between overhead power lines and adult hematological malignancies was investigated in a case-referent study by Youngson et al (22). Altogether 3144 cases with non-Hodgkin's lymphoma, acute lymphatic leukemia, chronic lymphatic leukemia, acute myeloid leukemia, and chronic myeloid leukemia were included in the study. Of them, the 1491 northwest residents were diagnosed in 1983—1985, whereas the 1653 Yorkshire residents were diagnosed in 1979—1985. Altogether 3144 cancer-free referents were randomly selected from inpatient hospital discharges and matched for gender, date of birth and diagnosis, and health district of residence. The magnetic fields for the five years preceding the date of diagnosis were calculated according to the distance and maximum load currents. Matched conditional logistic regression was employed for the cancer analysis for distance (cut-off points 25, 50, 75, and 100 m) and calculated magnetic field (cut-off points 0.01, 0.03, 0.10, 0.30, and 1.00 μT).

The risk estimates for hematological malignancies by decreasing distance (cut-off points 100 and 50 m) were 1.00 (2908 cases versus 2932 referents), 0.98 (99 cases versus 103 referents) and 1.29 (105 cases versus 79 referents). A test for trend for OR values over successive 25-m distance bands was statistically significant for Yorkshire ($P<0.05$), but not for the northwest or for both areas combined. The OR values by increasing magnetic field (cut-off points 0.01, 0.1, and 1.0 μT) were 1.00 (3015 cases versus 3019 referents), 0.98 (100 cases versus 102 referents), 1.10 (23 cases versus 21 referents), and 3.00 (6 cases versus 2 referents). All 95% confidence intervals included the OR of 1.00.

The Swedish study

Feychting & Ahlbom (25) conducted a nested case-referent study on the risks of leukemia and nervous system tumors for Swedish adults residing within 300 m of 220 or 400 kV power lines between 1960 and 1985. Altogether 325 cases of leukemia (residence near power lines for at least one year before diagnosis) were identified from the Swedish cancer register. Two referents per case were selected from the study base at the year of diagnosis of the case and were individually matched for gender, age, power line, and parish. Spot measurements and the calculation of annual average historical magnetic fields for 1958—1985 were used for the primary exposure assessment. The estimates for distance (with cut-off points of 50 and 100 m), measured and calculated magnetic fields (with cut-off points of 0.10 and 0.20 μT), and cumulative exposure to magnetic fields (with cut-off points of 1.00, 2.00, and 3.00 μT-years) were used in the statistical analyses.

The matched leukemia OR values for cumulative exposure were 1.0 (reference), 1.1, and 1.4 for the categories of <1.00, 1.00—1.99, and ≥ 2.00 μT-years. The respective figures were 1.0 (reference), 1.7 and 3.5 (95% CI 1.0—12.0) for AML; 1.0 (reference), 2.1 and 1.6 for CML; and 1.0 (reference), 1.0 and 1.0 for CLL. The unmatched results were also presented with the higher exposure cut-off point of 3.0 μT-years, which provided OR values of 1.5 for overall leukemia, 1.9 (95% CI 1.0—6.4) for AML, 2.7 for CML, and 1.2 for CLL. No excess leukemia risk was observed for magnetic field closest to time of diagnosis, spot measurements, or distance.

Summary

Overall, there are very few studies with any substantial information on residential magnetic fields and adult leukemia. These studies have observed no major increases in leukemia risk by magnetic field exposure (table 5). Some weaker excesses have, however, been observed for the leukemia risks of some selected subgroups. In one study (21), for instance, an excess of 100% was observed for leukemia among those living within 25 m or between 25 and 50 m of power lines; another study (22) observed an excess of 200% for those with magnetic fields of ≥ 1.0 μT; and yet another study (25) found an increase of 50% for those with cumulative exposure of ≥ 3.0 μT-years. The methodological limitations of these studies included small numbers and exposure misclassification.

Unresolved issues

According to the scientific literature, the following issues on magnetic fields and cancer thus remain unresolved and warrant further epidemiologic research. Hematopoietic tissues have been regarded as a possible target for magnetic fields. In the beginning of the present study (1988), there were practically no studies with substantial information regarding the question of residential magnetic fields and adult leukemia. Furthermore, an epidemiologic study may, despite the lack of a known carcinogenic mechanism, help to identify health hazards and define some general carcinogenic properties of an agent. Of them, time-related issues had been approached the most poorly in this area of research. The two major unresolved issues were, however, the assessment of exposure to magnetic fields and selection bias.

Assessment of magnetic fields

Exposure must precede the suspected outcome to qualify as a potential cause. Retrospective assessments of magnetic fields must rely either on concurrent measurements or on previous documents. Because the stability of measured magnetic fields over a long period of time is controversial, reliance on existing documents appeared to be a better choice. High-voltage power lines provided a field source which would (i) account — when present — for an important part of overall exposure in the vicinity of lines, (ii) have existed over an identifiable time period, and (iii) have some additional exposure data apart from the mere presence of a source of magnetic fields. Furthermore, it was feasible to calculate the residential magnetic fields in assessing the probability — if not the quantity — of excess exposure to magnetic fields generated by power lines.

Selection bias

Selection bias is an issue which was raised in the context of power lines and childhood cancer. The residential areas with low wiring codes have been described to be residentially more stable than the areas with high wiring codes (123). In at least one North American study (33), the cancer cases had less stable residences than the referents did, with the possible consequence that the selection of the referents may have introduced a spurious positive association between wiring code and childhood cancer. It seemed plausible that this type of problem might pertain also to studies of adult leukemia.

Objectives of the present study

The principal objective of this study was to examine the hypothesis that 50-Hz magnetic fields are leukemogenic in human adults. The more specific aims were as follows:

1. To study leukemia risk with respect to the calculated magnetic fields generated by high-voltage overhead power lines in Finland.
2. To investigate leukemia risk and exposures to magnetic fields with respect to dose-response and time-related factors.
3. To determine whether susceptibility to the effects of magnetic fields differs by leukemia subtype.

Material and methods

The cohort study included all Finnish people over 20 years of age, having lived any period of time in 1970—1989 within a distance of 500 m of 110, 220, and 400 kV overhead power lines in a calculated magnetic field of ≥ 0.01 µT in Finland. The study subjects (N = 383 700) entered the cohort on 1 January 1970 at the earliest or when they moved into an exposed building for the first time. The follow-up for cancer and the calculation of person-years began on 1 January 1974 or, if later, on the 20th birthday and ended at death or on 31 December 1990. In other words, every Finnish adult 20 years of age or more and having lived in the vicinity of an overhead transmission power line was followed for cancer, regardless of the later history of exposure to magnetic fields of power lines. The data collection of this study was based on several consecutive record linkages of nationwide data files (ie, the power-line data, the Central Population Register, the Finnish Cancer Registry, and the population census of 1970). One of them, the power-line data file, was created for the purpose of facilitating epidemiologic studies of power lines and cancer. In addition to the cohort study, a case-cohort study — nested in the study cohort — was also conducted using a larger selection of secondary exposure measures. Conduction of the case-cohort study was necessary to increase the flexibility of the data analyses.

Sources of data

Central Population Register

The Central Population Register is administered by the Population Register Center, and it is technically managed by the Finnish State Computer Centre (currently TT-Valtionpalvelut Oy). The Central Population Register has separate data files for individual persons and buildings. The link between the two is provided by a building code, which is unique for every building in Finland.

Person data files. In Finland, local parishes have recorded births, deaths, marriages, and emigrations and reported this information to the authorities since the 16th century. The person data files of the Finnish Central Population Register were started in 1971, and virtually all Finnish people alive since January 1974 are included in the active data files of this register. These people can be identified by personal identification codes unique for every resident in Finland; the codes include the date of birth, a three-digit running number given by the Population Register Center (odd for men and even for women), and a check digit. The person data files include, among other things, data on personal life history (dates of birth, marriage and death) and residential history (every address including building identification codes and official dates of moving in and out since 1984, along with a maximum of two addresses before 1984).

Register of buildings and individual premises. The register of buildings and individual premises was originally based on a set of questions in the questionnaire of the 1980 population census. The information has been updated regularly by housing authorities and authorities supervising local construction activities. This register is currently a nationwide data base containing detailed information, including location coordinates of each building's central point, on practically every building in Finland. The existence of location coordinates makes it possible to link Central Population Register data to other files containing numeric geographic information.

Power-line data

The studied power-line network covered 17 980 km, or 90% of the total length of 110—400 kV power lines in Finland in 1989 (figure 3). The respective numbers were 12 100 km (88%) for 110 kV lines, 2480 km (99%) for 220 kV lines, and 3400 km (100%) for 400 kV lines. The locations of the power lines were principally retrieved from the basic topographic maps of Finland (scale 1:20 000), which are based on aerial photographs. If a power line had been built after the completion of a basic map, power-line construction maps (scale 1:20 000) provided supplementary information on the location.

Power-line data, other than location, were obtained from the five Finnish power companies that operated, or had designed, these power lines (Imatran Voima Oy, Teollisuuden Voimansiirto Oy, Tampereen energialaitos, Oulun kaupungin energialaitos and Etelä-Pohjanmaan Voima Oy). Data on (operational or nominal) voltage, active and reactive power, and typical line-specific tower types were received for the calculation of magnetic flux densities. Some additional data items, such as actual locations of phase conductors and once per hour repeated recordings on power levels in a sample of 230 power lines, were used solely to validate the exposure assessment.

Finnish Cancer Registry

The Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, has collected data on all incident cancer cases and all cancer deaths in Finland since 1953. It receives notifications on cancer patients independently from hospitals, pathological and hematological laboratories, physicians, dentists, forensic autopsies, and death certificates. Since 1961, the National Board of Health has made the reporting of cancer cases compulsory. In 1989 cancer diagnoses were based on histological confirmation in 89% of the cases and solely on death certificates in 1.2% of the cases (124). In this study, the following data items of the summary record of the Finnish Cancer Registry were used for identifying leukemias (item 5 was needed solely to help to identify true malignant lesions diagnosed prior to the leukemia diagnosis, and it was used subsequently for the exclusion of the leukemia cases with prior cancers from the case-cohort analyses):

1. Personal identification number of the study subject.
2. Primary site, determined according to the code of the International Classification of Diseases from 1955, 7th revision (ICD-7), as modified and extended by the Finnish Cancer Registry.
3. Histology or cell type of cancer: code of the *Manual of Tumor Nomenclature Coding* (125).
4. Date of diagnosis (ie, date when the cancer was verified by a physician).

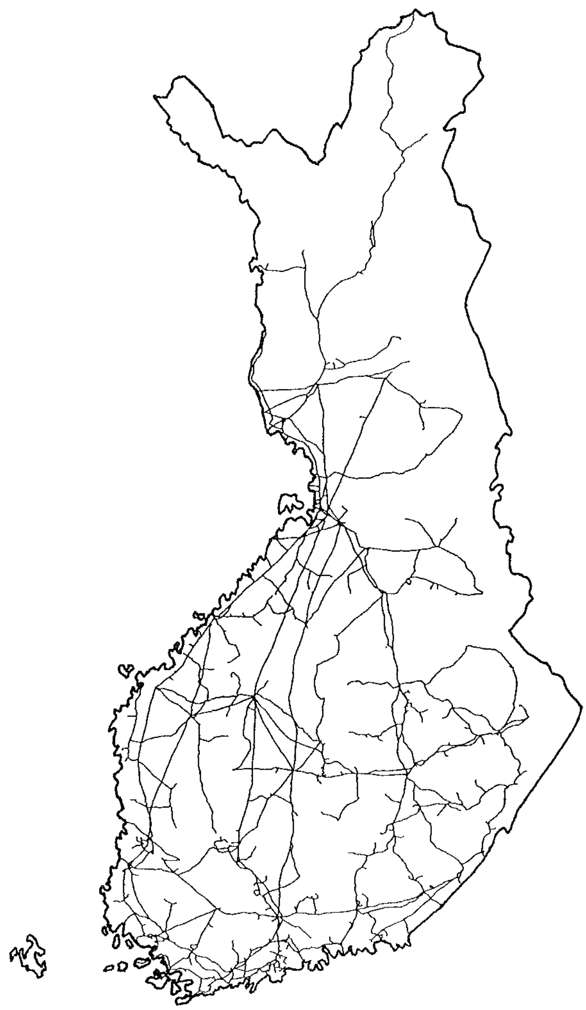

Figure 3. Finnish 110—400 kV power-line network included in the study.

5. Malignancy of the cancer as true malignant tumors; borderline tumors; in situ cancers; lesions such as basal-cell carcinoma of the skin, carcinoma in situ of the cervix uteri, and papilloma of the bladder, which are notified to the Finnish Cancer Registry but not usually included in the official cancer statistics.

Population census of 1970

An official population census was organized in Finland every five years between 1970 and 1990 by the Central Statistical Office of Finland (currently Statistics Finland) (126, 127). Everyone living in Finland on the census day (eg, 31 December 1970) was expected to complete a questionnaire including questions on family structure, living conditions, work, and the like. The questionnaires were coded and entered into the computer at the Central Statistical Office of Finland.

A social class classification, which was mainly based on the prestige of occupations, with four ordinary classes, was chosen for describing social class. Financially dependent persons (eg, housewives and students) were classified by the occupation of their supporter and economically active persons by their current or former occupation. The four social classes were defined as follows:

(I) Managers and other high administrative or clerical employees, farmers owning 50 or more hectares of land
(II) Lower administrative or clerical employees, small-scale entrepreneurs, farmers owning 15—49.9 hectares of land
(III) Skilled and specialized workers, farmers owning 5 to 14.9 hectares of land
(IV) Laborers, farm and forestry workers, institution inmates, farmers owning less than 5 hectares of land, pensioners whose former occupation was unknown.

Persons with an unknown social class (1.5% of the total population or 1.0% of the economically active population; mainly farmers and fishermen) were included in social class III.

The classification of occupations in the 1970 population census was based on the Nordic Classification of Occupations of 1963 and on the International Classification of Occupations, published by the International Labour Office in 1958. The first digit of the three-digit occupation code indicates the main occupational branch (eg, 6/7 manufacturing and construction work), the first two digits the occupational branch (66 electrical work), and all three digits together the specific occupation (664 telephone installers and repairmen).

The educational qualifications were documented with a one-digit code referring to each person's highest schooling level on the census date (31 December 1970). All educational periods longer than six months, as well as completion of compulsory education, secondary school, vocational school, university and equivalent levels, were considered in this ordinal classification.

The buildings in the 1970 population census were grouped into 10 categories with a one-digit code as follows: 1 = individual or duplex housing, 2 = terraced or row houses, 3 = apartment buildings, 4 = industrial sites, 5 = business premises, 6 = traffic-related buildings, 7 = schools, 8 = institutional buildings (hospitals, health care centers, prisons, etc), 9 = other official buildings (theaters, swimming pools, etc), and 10 = other buildings.

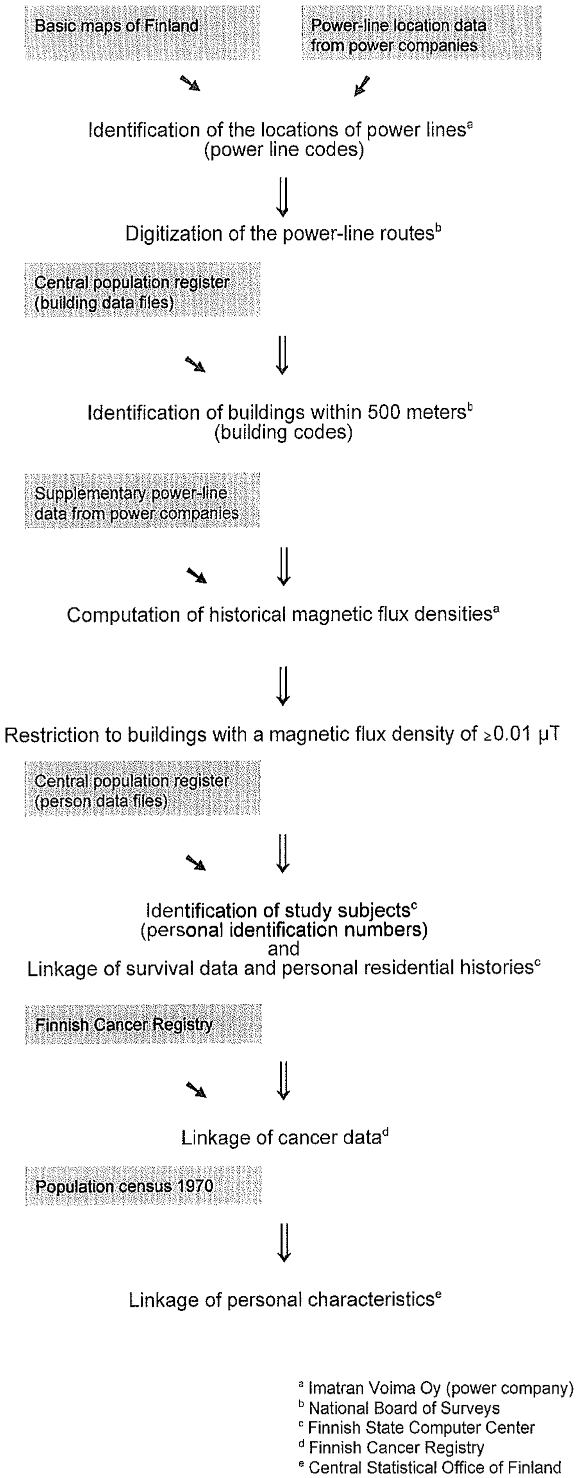

Figure 4. Principal steps of the data collection. The data sources are shown in boxes; the institutes responsible for the technical realization of each step are given in the footnotes.

Data collection and classification

Data collection process

The first step in this study project, collection of power-line data, began in 1989 and the last record linkages to the 1970 population census were done in 1994. The successive steps in the data collection are summarized in figure 4.

The locations of the power lines at the end of 1989 were verified on basic topographical maps (scale 1:20 000). The routes of the power lines were computerized using the Finnish geographic information system (FINGIS), of the National Board of Surveys (currently Karttakeskus Oy).

The computerized data on power lines were linked to the register of buildings and individual premises of the Central Population Register. The shortest distances between the power lines and the central points of the buildings were calculated by using the coordinates of both the buildings and the power lines. Buildings within 500 m of the power lines were identified.

The magnetic flux densities at the central points of each of these buildings were calculated for each of the years from 1970 through 1989 at Imatran Voima Oy (a power company). Buildings with an average annual magnetic field of ≥ 0.01 μT for one or more calendar years between 1970 and 1989 were included in the study (buildings with no such fields were excluded to decrease the economic costs of subsequent record linkages).

The building data files of the present study were then linked to the person data files of the Central Population Register. People who had lived in the buildings with a calculated magnetic field of ≥ 0.01 μT for any period between 1970 and 1989 were identified. They constituted the study cohort. The next step was to draw data on the cohort members' residential histories and deaths from the Central Population Register.

Data on incident cancers among the study cohort were linked from the Finnish Cancer Registry using the personal identification numbers.

The personal characteristics of the study subjects were mainly obtained from the data files of the 1970 population census by record linkage.

The summary data files contained information on a total of 383 745 Finnish people. Table 6 shows the contents of the files in more detail, including the original classification of each variable and its period of reference, the data source, and the purpose for which the variable was used in the course of the study.

Measures of exposure to magnetic fields of power lines

Calculation of magnetic flux densities. Average annual magnetic flux densities for the years 1970—1989 were calculated separately for each building using the computer program *Epidem, Imatran Voima Oy*. The input data

Table 6. Primary data at the personal level. [CPR-P = personal data files of the Central Population Register, PC70 = population census of 1970, CPR-B = building data files of the Central Population Register, IVO = power-line data files of Imatran Voima Oy (a Finnish power company), FCR = Finnish Cancer Registry]

Variable	Primary classification	Timing	Source	Further use in the study
Survival				
Date of birth	Continuous	Before 1990	CPR-P	Calculation of person-years/ control for confounding
Date of death	Continuous	Before 1991	CPR-P	Calculation of person-years
Date of moving abroad (the first time)	Continuous	Before 1994	PC70	Exclusion from case-cohort data
Residential history (all data items for each residential period)				
Dates of moving in and out of a building	Continuous	1970—1989	CPR-P	Exposure assessment
Municipality	Nominal	At first exposure	CPR-B	Control for confounding
Type of housing	Nominal	1970	PC70	Control for confounding
Exposure data				
Average magnetic flux density	Continuous	Annually, 1970—1989	IVO	Exposure assessment
Personal characteristics				
Social class	Ordinal (I, II, III, IV)	1970	PC70	Control for confounding
Education	Ordinal	1970	PC70	Control for confounding
Occupation	Nominal	1970	PC70	Restriction of analysis/ control for confounding
Marital status	Nominal (unmarried, married, living separated, divorced, widowed)	1970	PC70	Control for confounding
Cancer data (all data items for each primary cancer)				
Date of diagnosis	Continuous	1974—1990	FCR	Outcome definition
Primary site	Nominal	1974—1990	FCR	Outcome definition
Histological code	Nominal	1974—1990	FCR	Outcome definition
Malignancy code	Nominal	1974—1990	FCR	Identification of earlier primary cancers
Ordinal number of the primary cancer	Ordinal	Before 1991	FCR	Identification of earlier primary cancers

sets in this study included information on power-line identification code, annual average current, voltage, typical locations of phase conductors in power lines, and the distance between the power lines and the central points of the buildings.

Currents were calculated from operational or nominal voltages and from the active and reactive power of all power lines. Data on power-line currents (load flows) were collected by the following three methods:

1. Point estimates of average annual currents for 1984—1989 were generated by *PSS/E-18 Power System Simulator, Power Technologies Inc*
2. Existing load flow documents furnished corresponding power information for 1977—1983
3. Power data from 1977, corrected for completion years of power lines, served as estimates for 1970—1976. If several power lines were within 100 m of a building, the combined effect of all power lines was estimated on the assumption that the lines were parallel.

The computer program *Epidem* first calculated the vertical and horizontal vectorial phasor components of magnetic flux density (B) separately for each conductor and then summed up all the components to provide the root mean square of the magnetic flux density (B) at the observation point. Neglect of a third (ie, longitudinal) dimension is based on the assumption that the power lines are straight and go for a sufficient distance toward unity. The computation of magnetic flux densities was performed in the power company Imatran Voima Oy and has been presented elsewhere in more detail (128—130). The calculated magnetic flux densities were saved with the building identification codes in the magnetic flux density files.

Annual average magnetic field. The distributions of the subjects according to their average magnetic fields (in µT) for each of the calendar years of 1970 through 1989 were investigated using the personal level primary data. The number of persons with exposure to an average annual magnetic flux density of ≥ 0.01 µT increased fivefold from 1970 to 1989 (N = 31 524 in 1970, N = 118 395 in 1980, and N = 160 398 in 1989). The distributions of people by exposure have been given elsewhere in more detail (130, 131). The distribution of the magnetic flux density was skewed to the right with a median of 0.01 µT. The statistics of the average annual magnetic flux density in 1989 are displayed in table 7. Most of the quantiles were almost stable between 1970 and 1989, with the exception of the 99th percentile, which decreased from 0.61 µT in 1970 to 0.51 µT in 1980 and further to 0.48 µT in 1989. However, the maximal magnetic flux density increased correspondingly from 3.9 µT to 5.7 µT and further to 8.5 µT. Considering the expected background magnetic flux density of 0.1 µT in Finnish homes, and the skewed distribution of the magnetic fields, the cut-off points of magnetic flux density were set at 0.10 µT, 0.20 µT, and 0.30 µT.

Table 7. Average annual magnetic field exposure (1989) and cumulative exposure (1970—1989) in Finland.

Exposure statistic	Magnetic field (µT)	Cumulative exposure (µT-years)
Mean	0.05	0.25
25th percentile	0.01	0.02
Median	0.01	0.05
75th percentile	0.03	0.16
90th percentile	0.09	0.48
95th percentile	0.18	0.94
99th percentile	0.48	3.38
Maximum	8.5	80.7

Cumulative exposure. Cumulative exposure (in µT-years) provided the study with a summary measure for the overall exposure to the residential magnetic fields of power lines. For the purposes of this study, cumulative exposure was theoretically defined as the sum of the products of the average exposure and the duration of such exposure (in µT-years). In practice, cumulative exposure was estimated by summing up the average annual magnetic flux densities, only the exposures preceding the leukemia diagnosis being taken into account.

Some statistics for cumulative exposure (calculated to correspond with the situation on 31 December 1989) summarize the exposure histories between 1970 and 1989 (table 7). The mean cumulative exposure was 0.25 µT-years, but the distribution was highly skewed to the right. The highest cumulative exposure, 80.7 µT-years, was received by a person having lived in a magnetic field of 7.3 µT over more than 10 years. The people with the four second highest cumulative exposures, all 67.8 µT-years, had been living in a magnetic field of 3.4 µT, on the average, over a period of 20 years.

The exposure cut-off points of 0.40, 1.00, and 2.00 µT-years were chosen a priori for the cohort study. An additional cut-off point of 0.20 µT-years was set for the case-cohort study to create a separate exposure category for the subjects who had lived in a slightly increased magnetic field over a short period of time (eg, in 0.20 µT between 1 and 2 years).

Other exposure measures. Other measures of exposure to residential magnetic fields were derived from the personal exposure histories to investigate leukemia in relation to dose-response and time-related factors. The magnitude of exposure (in µT) was assessed with a series of measures for annual average magnetic fields, with the highest average magnetic field, and with the highest average magnetic fields during three mutually exclusive exposure periods (0—4, 5—9, or ≥ 10 years before diagnosis). As to the timing of exposure, measures were created for cumulative exposures (in μT-years) over the three exposure periods, as well as for time since first exposure (in years) (only exposures greater than or equal to an annual average magnetic field of ≥0.10 μT being used), age at first exposure (in years), duration of exposure (in years), and time since last exposure (in years).

Hypothetical connections between the exposure measures and leukemogenesis. The exposure measures of the present study were thought to assess the various aspects of leukemogenesis as follows: (i) *cumulative exposure* to provide an estimate for the overall effect of magnitude and length of exposure to magnetic fields of power lines, (ii) *highest annual average magnetic field* to measure dose-response and *average annual magnetic fields* to specify the timing of dose-response, (iii) *cumulative exposure over the mutually exclusive exposure periods* together with *time since first exposure* and *age at first exposure* to address the question of induction time, (iv) *duration of exposure* to explore whether prolongation of exposure increases the risk of leukemia, and (v) *time since last exposure* to investigate what happens to the risk of leukemia after the cessation of exposure to magnetic fields (ie, reversibility of the possible effect).

Classification of leukemia

The outcome events for the leukemia subtype analyses were grouped as follows: (i) acute myeloid leukemia (AML), (ii) acute lymphatic leukemia (ALL), (iii) chronic lymphatic leukemia (CLL), and (iv) other types of leukemia combined [chronic myeloid leukemia (CML), unspecified myeloid leukemia, unspecified lymphatic leukemia, monocytic leukemia, and hairy-cell leukemia]. This subtype selection was made because AML and CLL are the two most common leukemia subtypes in Finland and ALL was of special interest due to the childhood cancer studies. In the course of the present study, it was decided to consider the additional subgroup CML in the case-cohort analyses. Because the cohort analyses using grouped data sets had been performed before this decision, CML was not available as a separated entity for the cohort analyses.

Classification of covariates

Surrogate measure of occupational magnetic fields. The measured magnetic field exceeds 0.2 μT in several occupations and workplaces. It therefore seemed feasible that magnetic fields from occupational sources might introduce a misclassification of exposure to magnetic fields. There was thus a need to create a surrogate measure for estimating the probability of exposure to occupational magnetic fields in this study.

There were altogether 339 three-digit codes for occupations in the population census in 1970 (126, 127). Two researchers with expertise on magnetic field measurements were asked to assign the occupational codes into three categories according to the likelihood of exposure to magnetic fields from occupational sources. The categories were (i) no exposure, (ii) possible (or potential) exposure, and (iii) probable exposure to ELF magnetic fields from occupational sources.

The two classifiers agreed originally on the exposure category for 70% (N = 238) of the codes. The proportion of agreement for each individual category of occupational exposure was calculated by dividing the number of similarly-classified codes in each category by the numbers of codes classified into this category. The proportions are given in percentages. The proportion of agreement was higher (83%) for the category of "no exposure" and lower for the categories of "possible" (38%) and "probable exposure" (12%). The kappa coefficient (κ) was calculated according to Cohen (132) to measure the proportion of agreement corrected for chance; the kappa coefficient was only 0.23. It was therefore decided to make the classification criteria more precise. The classifiers were contacted again and the prerequisites of a valid classification were discussed. The final classification of the 101 codes originally disagreed upon was arrived at by a consensus of both classifiers and the author.

The principal prerequisite for assigning an occupational code into the three categories turned out to be that there should be magnetic field measurements (preferably made in some Nordic country with fairly similar work conditions and corresponding occupational categories) indicating an increased magnetic field either in the occupation or largely within the industry in question. The choice between the categories of possible and probable exposure was principally based on measured magnetic field levels.

There was, however, no explicit cut-off point for exposure because some other less quantifiable and less objective aspects also had to be considered in the assignment of the codes. If occupational codes referred to heterogeneous groups of workers with undoubtedly different work methods (eg, welders, metal smelting furnacemen, and truck drivers) some of whom were probably exposed to magnetic fields from an occupational source whereas others in the same occupation were likely not, the occupational code was assigned to the category of possible exposure (instead of probable exposure as suggested by one of the original classifications).

On the other hand, if there was an obvious reason to suspect that the magnetic field level had changed in the occupation remarkably since the beginning of the 1970s, the (hypothetical) situation in the 1970s (with no field measurements) was considered more important than the more recent situation. For instance, some recent measurements indicated that cashiers might be exposed to unexceptionally high magnetic fields (11). The exposure source was thought to be the nearby security systems with electrical wiring (not the cash registers) — which have recently become more common — and cashiers were classified as "not likely" exposed. Another example is locomotive engineers who were — despite some current measurements indicating increased magnetic field levels — classified only as possibly (and not probably) exposed. The reason for this was the relatively recent electrification of the Finnish railways (the first track was electrified as late as 1969 and the first main line from Helsinki to Seinäjoki in 1975; more than 80% of the railway network was still not electrified in 1980) (Bergström M, Museum of the Finnish Railways, personal communication in 1996).

Appendix 2 shows the final assignment of the occupational codes of the population census of 1970 into the categories of possible (95 codes) and probable (16 codes) exposure to ELF magnetic fields.

Municipality status. Codes for the municipality status at first exposure were classified into "urban" and "rural" using, primarily, the official classification of municipality status on 1 January 1977 (133). If the municipality had "vanished" due to a municipality incorporation, the code of the new municipality was applied for the classification. The 1977 municipality status appeared to provide a useful surrogate for urban- and rural-related differences. First, the year 1977 was the only time for changes in the official classification of municipalities between 1974 and 1986 (134). Second, the selection of an earlier — or a more recent — municipality classification could easily have led into an apparent contradiction between the municipality status and the actual environment. For instance, the city of Vantaa, which is nowadays an essential part of the "greater Helsinki area," has been classified as "a city" only since 1974. On the other hand, several smaller villages (eg, Ähtäri and Kuhmo) ceased to be "rural communities" in 1986.

Other covariates. The original categories of the 1970 census as such were applied for social class and marital status (see the section on the Population census of 1970), with the exception of the marital categories for separated and divorced, which were combined. As to educational qualifications, the relevant one-digit codes of the 1970 census were classified into the categories of (i) primary education (compulsory schooling or equivalent) or less, (ii) secondary education (completion of secondary school or a vocational school), and (iii) tertiary education (university degree or equivalent). With regard to housing type, buildings were classified into detached houses and other buildings. As to the remaining covariates, the subjects were also classified by gender, age (continuous or 5-year age groups), and calendar period of observation (1974—1981, 1982—1990).

Definition of the subjects and leukemia cases

The study cohort included all Finnish people having lived in Finland any period of time in 1970—1989 within a distance of 500 m of 110, 220, and 400 kV power lines in a calculated annual average magnetic field of ≥ 0.01 µT. The follow-up for cancer and the calculation of person-years began on 1 January 1974, or, if later, on the 20th birthday and ended at death or on 31 December 1990.

The subjects of the cohort analyses accumulated over 2.5 million person-years during the follow-up for cancer in 1974—1990, 48% by the men and 52% by the women. The distributions of the person-years are shown in table 8.

The cases for the case-cohort study (135) were selected from the cohort study files. Prior real cancers and having emigrated from Finland before the date of diagnosis were not allowed either for the cases or the referents. Ten referents from among the remaining cohort members were successfully matched to each case, with the exception of two cases for whom only nine referents were found. The matching criteria were gender, age at diagnosis (± 1 year), and alive in the year of diagnosis of leukemia.

A total of 203 cases of leukemia were observed in the cohort during 1974—1990, whereas 196 leukemia cases (and 1958 referents) were considered eligible for the case-cohort analyses. The actual number of leukemias in the case-cohort data was smaller than that in the cohort data for two main reasons (table 9). First, the use of two exclusion criteria removed 12 cases. Second, the continuous process of updating the Finnish Cancer Registry data, also during the period between the two subsequent record linkages (on 7 January 1993 for the cohort data and on 4 August 1994 for the case-cohort data), led to some diagnostic changes with regard to the leukemia status of the subjects. One leukemia case had been coded as undefined lymphoma; the dates of diagnosis for two leukemias were predated so that the subjects had in fact not entered the cohort before the leukemia diagnosis. Eight new leukemias (7 CLL and 1 AML) were registered by the Finnish Cancer Registry between the two linkages.

Of the observed leukemias, some 36% was CLL, 32% was AML, and 6% was ALL; 27% was of unknown or some other cell type (table 10).

The characteristics of the cases and referents are presented in table 11 in more detail.

Table 8. Person-years of the cohort (N = 2.5 million).

Variable	Person-years	
	Number (in thousands)	%
Cumulative exposure		
< 0.40 µT-years	2263.5	89.0
0.40—0.99 µT-years	170.2	6.7
1.00—1.99 µT-years	61.7	2.4
≥ 2.00 µT-years	47.8	1.9
Gender		
Men	1222.8	48.1
Women	1320.3	51.9
Age		
20—34 years	977.5	38.4
35—49 years	811.7	31.9
50—64 years	466.7	18.4
≥ 65 years	287.2	11.2
Calendar period of observation		
1974—1981	643.5	25.3
1982—1989	1899.6	74.7
Municipality		
Urban	1983.0	78.0
Rural	560.1	22.0
Social class[a]		
I	177.5	7.0
II	639.6	25.2
III	1283.6	50.5
IV	322.6	12.7
Missing	119.8	4.7
Education		
Primary or less	1886.9	74.2
Secondary	496.6	19.5
Tertiary	69.7	2.7
Missing	89.9	3.5
Marital status		
Unmarried	1205.2	47.4
Married	1149.5	45.2
Divorced	46.4	1.8
Widowed	68.3	2.7
Missing	73.7	2.9
Occupational exposure to magnetic fields		
Not exposed	2063.4	81.1
Possibly exposed	442.8	17.4
Probably exposed	36.9	1.5
Type of housing		
House	1451.3	57.1
Apartment building	911.9	35.9
Other or missing	179.9	7.1

[a] See the text as for an explanation of the classes.

Table 9. Reasons for the difference in the numbers of leukemia cases in the case-cohort data and the cohort data.

Reason for the difference in the numbers of leukemia cases	Number
Cases in the cohort data	203
Added exclusion criteria	
Prior malignancy	−3
Emigration from country	−9
Diagnostic changes	
Rediagnosis	−1
Predating of previous diagnosis	−2
Delay in reporting to the Finnish Cancer Registry	+8
Cases in the case-cohort data	196

Table 10. Leukemia cases in the cohort versus case-cohort data by subtype.

Subtype	Cohort (N = 203)		Case-cohort (N = 196)	
	N	%	N	%
Acute myeloid leukemia	64	31.5	60	30.6
Acute lymphatic leukemia	12	5.9	12	6.1
Chronic lymphatic leukemia	72	35.5	73	37.2
Other type of leukemia	55	27.1	51[a]	26.0

[a] 30 cases of chronic myeloid leukemia.

Table 11. Characteristics of the cases and referents.

Variable	Cases (N=196)		Referents (N=1958)	
	Number	%	Number	%
Gender				
Men	106	54	1058	54
Women	90	46	900	46
Age at diagnosis				
20—34 years	16	8	160	8
35—49 years	33	17	330	17
50—64 years	44	23	440	23
≥ 65 years	103	53	1028	53
Calendar period of observation				
1974—1981	59	30	590	30
1982—1989	137	70	1368	70
Municipality				
Urban	154	79	1394	72
Rural	42	21	564	29
Social class				
I	14	7	121	6
II	44	23	418	21
III	98	50	1014	52
IV	34	17	318	16
Missing	6	3	87	4
Education				
Primary or less	158	81	1534	78
Secondary	28	14	302	15
Tertiary	8	4	81	4
Missing	2	1	4	0
Marital status				
Unmarried	36	18	358	18
Married	123	63	1288	66
Divorced	7	4	60	3
Widowed	28	14	210	11
Missing	2	1	42	2
Occupational exposure to magnetic fields				
Not exposed	149	76	1530	78
Possibly exposed	44	23	393	20
Probably exposed	3	2	35	2
Type of housing				
House	119	61	1240	63
Apartment building	63	32	614	32
Other or missing	9	5	104	5

Statistical methods

Cohort analyses

Grouped data sets. The study subjects were classified into categories according to gender, age (5-year age groups), calendar period of observation (1974—1981, 1982—1990), type of municipality (urban, rural), type of housing (house, other), social class (I, II, III, IV, other), education (primary, secondary, tertiary), marital status (unmarried, married, separated or divorced, widowed), occupational exposure to magnetic fields (no exposure, possible exposure, probable exposure), and cumulative exposure (< 0.40, 0.40—0.99, 1.00—1.99, ≥ 2.00 μT-years).

This data file had to be made smaller by combining original categories to allow its use for statistical modeling with the PC-based software available for this study. Therefore five smaller data sets were created, all of which retained the original classification by gender, age, calendar period, and type of municipality. In addition, the classification was retained by social class in grouped data set 1, by marital status in set 2, by education in set 3, by occupational exposure in set 4, and by type of housing in set 5.

Standardized incidence ratio analyses. The calculation of person-years of observation began for each category on 1 January 1974, at the earliest, or on the 20th birthday. The calculation ended at death or on 31 December 1990, whichever occurred first. The observed numbers of leukemia cases were counted for the respective categories. The expected numbers of cases were calculated by multiplying the stratum-specific numbers of person-years by the corresponding cancer incidences in Finland. The standardized incidence ratios (SIR) were calculated by dividing the observed number of cases by the corresponding expected number. The exact 95% confidence intervals were defined using the computer program *Confidence Interval Analysis, British Medical Journal*, which makes the assumption of Poisson distribution for the observed number of cases.

Table 12. Classifications of the covariates used in the statistical analyses.

Covariate	Levels
Gender	1 = men 2 = women
Age for each five-year observation period	a) five-year age groups or b) continuous
Calendar period of observation	1 = 1974—1981 2 = 1982—1990
Residential municipality at first exposure	1 = urban 2 = rural
Social class in 1970	1 = I—II 2 = III—IV
Marital status in 1970	1 = unmarried 2 = married 3 = divorced 4 = widowed
Education in 1970	1 = primary or less 2 = secondary or tertiary
Occupational exposure to magnetic fields	0 = no exposure 1 = possible or probable exposure
Residence at first exposure	1 = house 2 = other

Incidence rate ratio analyses. A multiplicative Poisson regression was employed using the *Amfit* program of the software package *Epicure, HiroSoft* for the analyses of incidence rate ratio (IRR). A default model (see the first model in the list below) with cumulative exposure was fitted first. The evaluation of the goodness-of-fit of this model was first made by stepwise addition to the model of covariate terms for gender, age, calendar period, type of municipality, social class, marital status, education, occupational exposure to magnetic fields, and type of housing (table 12). Exposure and age were treated as both continuous and polytomous variables; exposure was also used as a dichotomous variable. The calculated means of cumulative exposure within each exposure category (the means were 0.077, 0.62, 1.38, and 5.04 μT-years for the categories of < 0.40, 0.40—0.99, 1.00—1.99, and ≥ 2.00 μT-years, respectively) were used as continuous (numerical) estimates of exposure; with regard to age, the midpoint of each category served as the continuous estimate. An attempt was also made to add the age square term when a continuous age variable was chosen. The significance of a variable was assessed by a likelihood ratio test. The criterion of statistical significance was set at the 10% level, the significant variables being included in the final model. The possibility of effect modification by gender, age, and municipality was investigated by fitting the corresponding interaction term.

A variety of multiplicative, additive relative risk, and additive models was attempted for the cohort data according to Breslow & Day (136) as follows: (i) $RR(x) = \exp(\beta)$ (the default multiplicative model), (ii) $RR(x) = \exp(\beta x)$, (iii) $RR(x) = \exp(\beta x+\gamma x^2)$, (iv) $RR(x) = 1+\beta x$, (v) $RR(x) = 1+\beta x+\gamma x^2$, and (vi) $ER = \beta x$.

This selection of alternative models applied to the terms for exposure; multiplicative Poisson regression was employed solely to take the covariates into account. The fits of all the models were compared by examining the deviances; the effect of the model selection on the risk estimates was also studied. Modeling of the observed and expected numbers was attempted for the default model with cumulative exposure.

The goodness-of-fit for the selected multiplicative model versus additive model was evaluated further by the examination of residuals. The fitted values of the leukemia cases, deviance residuals (137), and hat matrix diagonals (137) were computed using the cohort data, on the assumption of fully parametric models with cumulative exposure, gender, age, and municipality. Deviance residuals were plotted versus fitted values to look for trends or patterns in the data. Hat matrices were plotted versus record index numbers to investigate whether some data records might have had an undue influence on the fit. The records were interpreted to be of great influence when the corresponding hat matrix diagonal was in excess of 2p/n, where p is the number of parameters in the model and n is the number of records in the data set (137). The influence of such a record on the results was studied by excluding the data points from the analysis.

Case-cohort analyses

A conditional logistic Poisson regression was employed to explore the effect of magnetic field exposure on leukemia risk in more detail. The exposure assessment in the cohort analyses had been based solely on cumulative exposure, whereas several new exposure measures were introduced for the statistical analyses of the case-cohort data, because, in the course of the study, it turned out to be more effective to run the more-detailed analyses using a case-cohort data set than a grouped cohort data set.

The various exposure measures in the case-cohort analyses were the following: (i) cumulative exposure to magnetic fields overall (continuous and with cut-off points of 0.20, 0.40, 1.00, and 2.00 μT-years) and cumulative exposure obtained (ii) 0—4 years before diagnosis, (iii) 5—9 years before diagnosis and (iv) ≥ 10 years before diagnosis, (v) annual average magnetic fields 1 through 20 years before diagnosis (continuous and with cut-off points of 0.10, 0.20, and 0.30 μT), (vi) the highest annual average magnetic field ever and the highest annual average magnetic field obtained (vii) 0—4 years before diagnosis, (viii) 5—9 years before diagnosis and (ix) ≥ 10 years before diagnosis, (x) age at first exposure to the annual average magnetic field of ≥n μT (continuous or with cut-off points of 35, 50, and 65 years of age), (xi) duration of exposure to an annual average magnetic field of ≥n μT (continuous or with cut-off points of 3, 6, 9, and 12 years), (xii) time since first exposure to an annual average magnetic field of ≥n μT (continuous or with cut-off points of 3, 6, 9, and 12 years), and (xiii) time since last exposure to an annual average magnetic field of ≥n μT (continuous or with cut-off points of 3, 6, 9, and 12 years).

The models were fitted along the same guidelines as has already been described using the *Pecan* program of the software package *Epicure, HiroSoft*. However, the model-building strategy was different from the incidence rate ratio analyses with regard to the first step, which was to fit the full model with main effect terms for exposure, municipality, social class, marital status, education, occupational exposure to magnetic fields, and type of housing all at once. The standardized regression coefficients $Z_1 = \beta/SE(\beta)$ corresponding to each term were calculated (β referring to the regression coefficient and $SE(\beta)$ to its standard error, both estimated from the model). They were used in a T-test (138) for an overview of the importance of various covariates in the full model. When one or more terms for a covariate were significant, the covariate was included in the final model. This significance was checked by an alternative approach by adding the sets of terms for each covariate and performing corresponding significance testing by a likelihood ratio test. The significant covariates were accepted for inclusion in the final model. The estimates of relative risk and 95% confidence intervals were provided from this model.

Results

In the first part of this section, the leukemia incidence rates of the study cohort have been presented and compared with the respective national rates. The behavior of leukemia risk in the various covariate categories has then been explored in more detail. The latter part of this section focuses on the actual study hypothesis. Risk from all forms of leukemia has been studied in relation to the *overall exposure to magnetic fields of power lines*. The accuracy of this principal result has then been ascertained by comparing the results obtained by two alternative study designs and by several types of statistical models. More specific exposure measures have finally been attempted to evaluate some of the principal aspects of leukemogenesis in relation to magnetic fields, that is, in case such a relationship exists. The risk of leukemia in association with magnetic field exposure has also been presented by the various covariate categories and, whenever feasible, also by leukemia subtype.

Descriptive epidemiology of leukemia

Incidence rates

The incidence rate of leukemia was calculated to be 8.0 per 10^5 person-years for the cohort and 8.4 for the whole of Finland (the latter adjusted for gender and age to the cohort population, with weights taken from the person-years of observation in the cohort). The figures were 8.9

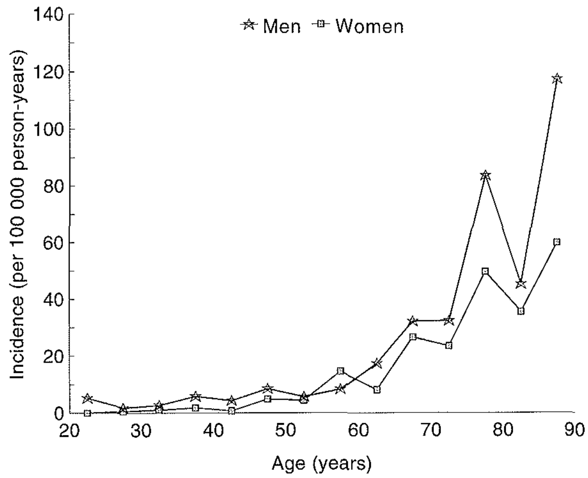

Figure 5. Incidence rates for leukemia per 1 million person-years in 1974—1990 by gender.

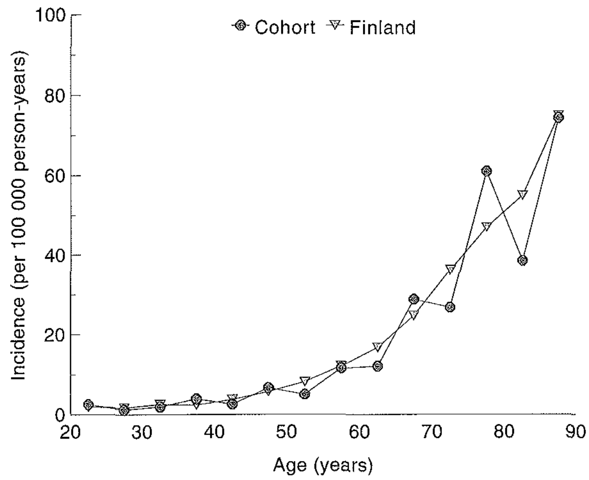

Figure 6. Age-specific incidence rates for leukemia per 1 million person-years in the study cohort and in the general Finnish population in 1974—1990.

Table 13. Leukemia risk in the study cohort by subtype. (O = observed number of leukemia cases, E = expected number of leukemia cases based on corresponding gender-, age-, and calendar-year-specific incidence rates in Finland, SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Subtype	O	E	SIR	95% CI
Acute myeloid leukemia	64	69.0	0.93	0.71—1.18
Acute lymphatic leukemia	12	16.3	0.74	0.38—1.29
Chronic lymphatic leukemia	72	70.2	1.03	0.80—1.29
Other type of leukemia	55	59.1	0.93	0.70—1.21
Combinations				
Lymphatic leukemia	84	86.5	0.97	0.78—1.20
Nonlymphatic leukemia	119	128.1	0.93	0.77—1.11
Acute leukemia	76	85.4	0.89	0.70—1.11
Nonacute leukemia	127	129.3	0.98	0.82—1.17
Total	203	214.6	0.95	0.82—1.09

and 9.4 for the men and 7.1 and 7.5 for the women, respectively. The age-specific incidence rates of leukemia were higher for the men than for the women of the cohort, with the exception of the 55 to 59-year age group (figure 5).

The age-specific incidence rates for the entire cohort followed the same pattern as the incidence rates for Finland (figure 6).

The SIR for leukemia in the whole cohort was 0.95 with a 95% CI of 0.82—1.09. The category-specific SIR values (with the 95% CI values) were all at the same level when calculated by gender or calendar period: men: 0.94 (95% CI 0.78—1.14); women: 0.95 (95% CI 0.77—1.16); calendar period 1974—1981: 0.98 (95% CI 0.75—1.25); and calendar period 1982—1990: 0.93 (95% CI 0.79—1.10). None of the SIR values for leukemia subtypes in the entire cohort differed significantly from unity (table 13).

Covariates as determinants of leukemia risk

Overall, gender, age, and municipality had a statistically significant effect on leukemia risk when specific risks for the covariate categories were compared within the cohort (table 14). The observed risk was almost 40% lower for the women than for the men. The relative risk (RR) for leukemia was estimated to increase by 7% per year (IRR per year 1.07, 95% CI 1.06—1.08) with age. Residing in rural areas decreased the leukemia risk by over 30%, compared with residing in an urban area. The other covariates did not have a statistically significant effect on leukemia risk. This result was confirmed by fitting analogous models to the case-cohort data.

Summary

The incidence rate of leukemia was somewhat lower in the whole cohort than in the general Finnish population, but the difference could have been due chance. This finding was consistent for both genders, for the two calendar periods of observation, and for the subtypes of leukemia other than CLL (the SIR of CLL was equal to unity). The age-incidence pattern for leukemia in the study cohort was parallel to that in the general Finnish population. Of the studied covariates, gender, age and municipality were found to be statistically significant determinants of leukemia risk.

Risk of total leukemia by magnetic field exposure

Distribution of the leukemia cases by exposure

A total of 203 cases of leukemia were observed in the study cohort; 196 cases were considered eligible for the case-cohort analyses. (See the section on the definition

Table 14. Leukemia risk in the cohort and case-cohort setting by covariate and risk estimate. (SIR = standardized incidence ratio, 95% CI = 95% confidence interval, IRR = incidence rate ratio, OR = odds ratio)

Covariate	Cohort				Case-cohort	
	SIR[a]	95% CI	IRR[b]	95% CI	OR[c]	95% CI
Gender						
Men	0.94	0.78—1.14	1.00	.	.[d]	.
Women	0.95	0.77—1.16	0.61	0.46—0.81	.	.
Age						
20—34 years	0.88	0.52—1.39	1.00	.	.	.
35—49 years	1.12	0.78—1.57	2.26	1.28—4.00	.	.
50—64 years	0.77	0.56—1.04	5.10	2.94—8.85	.	.
≥ 65 years	1.00	0.82—1.20	22.1	13.4—36.5	.	.
Change per year	.	.	1.07	1.06—1.08	.	.
Calendar period of observation						
1974—1981	0.98	0.75—1.25	1.00	.	.	.
1982—1990	0.93	0.79—1.10	0.83	0.61—1.12	.	.
Municipality						
Urban	1.03	0.88—1.20	1.00	.	1.00	.
Rural	0.72	0.52—0.98	0.70	0.50—0.99	0.66	0.45—0.97
Social class[e]						
I	1.20	0.68—1.92	1.00	.	1.00	.
II	1.02	0.76—1.36	0.89	0.50—1.57	0.83	0.38—1.82
III	0.87	0.70—1.06	0.77	0.45—1.30	0.72	0.33—1.56
IV	1.10	0.77—1.52	0.98	0.54—1.77	0.76	0.33—1.77
Education						
Primary or less	0.98	0.83—1.14	1.00	.	1.00	.
Secondary	0.84	0.56—1.21	0.79	0.53—1.19	0.84	0.52—1.34
Tertiary	0.45	0.055—1.64	0.44	0.11—1.79	0.81	0.31—2.13
Marital status						
Unmarried	0.91	0.64—1.25	1.00	.	1.00	.
Married	0.91	0.76—1.08	1.08	0.72—1.60	0.93	0.54—1.60
Divorced	1.07	0.43—2.21	1.25	0.55—2.86	1.15	0.44—2.96
Widowed	1.33	0.88—1.92	1.63	0.91—2.92	1.47	0.75—2.91
Occupational exposure to magnetic fields						
Not exposed	0.94	0.80—1.10	1.00	.	1.00	.
Possibly exposed	0.96	0.69—1.31	1.00	0.71—1.42	1.20	0.81—1.77
Probably exposed	0.97	0.20—2.82	0.95	0.30—3.00	0.90	0.27—3.00
Type of housing						
House	0.93	0.77—1.11	1.00	.	1.00	.
Terraced or row houses, apartment buildings	1.05	0.82—1.32	1.00	0.74—1.36	0.89	0.63—1.25
Other	0.57	0.23—1.17	0.57	0.27—1.23	0.98	0.43—2.22

[a] Calculated from the cohort data adjusting for the effects of gender, age, and calendar period. Compares the risk of leukemia in the cohort to the risk in the general Finnish population.
[b] Calculated from cohort data adjusting for the effects of gender, age, calendar period, and municipality. Compares the risk of leukemia in the specific (covariate) category to the base-line category (which is internal to the cohort). IRR = 1.00 indicates base-line category.
[c] Calculated from matched case-cohort data adjusting for the effects of other covariates; OR = 1.00 indicates base-line category.
[d] Matching for gender, age at diagnosis, and calendar year of diagnosis.
[e] See the text as for explanation of the classes.

of the subjects and leukemia cases on page 26). The number of leukemia cases with increased exposure to magnetic fields was rather small (tables 15, 16, and 17); for example, only 24 leukemia cases in the cohort data (12%) and 30 cases in the case-cohort data (15%) had a cumulative exposure of ≥ 0.40 µT-years. (The number of exposed cases is smaller in the cohort data because of the assumption of a one-year time lag between cumulative exposure and date of diagnosis. No such assumption was made for the case-cohort analyses.) The number of exposed cases was even smaller, with a higher exposure cut-off point, with other exposure measures, and for leukemia subtypes.

The leukemia subtypes with the greatest numbers of exposed cases were CLL (eg, 12 cases with ≥ 0.40 µT-

Table 15. Cases of leukemia by subtype and cumulative exposure level in the cohort data.

Cumulative exposure	Acute myeloid leukemia	Acute lymphatic leukemia	Chronic lymphatic leukemia	Other leukemia	Total
< 0.40 µT-years	58	10	60	51	179
0.40—0.99 µT-years	6	1	6	2	15
1.00—1.99 µT-years	—	1	3	1	5
≥ 2.00 µT-years	—	—	3	1	4
Total	64	12	72	55	203

Table 16. Cases of leukemia by subtype and exposure level in the case-cohort data. Distributions of exposure measures for all the subjects.

Exposure	Acute myeloid leukemia	Acute lymphatic leukemia	Chronic myeloid leukemia	Chronic lymphatic leukemia	Other leukemia	Total
Cumulative exposure						
< 0.20 μT-years	44	6	25	50	18	143
0.20—0.39 μT-years	7	4	2	9	1	23
0.40—0.99 μT-years	9	1	3	8	—	21
1.00—1.99 μT-years	—	1	—	3	1	5
≥ 2.00 μT-years	—	—	—	3	1	4
Highest magnetic field						
< 0.10 μT	55	8	29	65	19	176
0.10—0.19 μT	4	2	1	5	1	13
0.20—0.29 μT	—	2	—	1	1	4
≥ 0.30 μT	1	—	—	2	—	3
Duration of exposure (to magnetic fields of ≥ 0.10 μT)						
< 3 years	59	10	29	67	20	185
3—5 years	1	2	1	1	—	5
6—8 years	—	—	—	1	—	1
9—11 years	—	—	—	1	—	1
≥ 12 years	—	—	—	3	1	4
Total	60	12	30	73	21	196

Table 17. *Cases of leukemia by subtype and exposure level in the case-cohort data. Distributions of the exposure measures restricted to the subjects with the highest magnetic field of ≥ 0.10 μT.*

Exposure	Acute myeloid leukemia	Acute lymphatic leukemia	Chronic myeloid leukemia	Chronic lymphatic leukemia	Other leukemia	Total
Age at first exposure (to magnetic fields of ≥ 0.10 μT)						
20—34 years	2	2	—	—	—	4
35—49 years	—	1	—	2	—	3
50—64 years	2	1	1	3	1	8
≥ 65 years	1	—	—	3	1	5
Time since first exposure (to magnetic fields of ≥ 0.10 μT)						
< 3 years	2	—	—	—	—	2
3—5 years	1	2	1	2	1	7
6—8 years	1	2	—	1	—	4
9—11 years	1	—	—	1	—	2
≥ 12 years	—	—	—	4	1	5
Time since last exposure (to magnetic fields of ≥ 0.10 μT)						
< 3 years	3	2	1	5	2	13
3—5 years	1	1	—	1	—	3
6—8 years	—	1	—	1	—	2
9—11 years	1	—	—	1	—	2
≥ 12 years	—	—	—	—	—	—
Total	5	4	1	8	2	20

years in the cohort data and 14 in the case-cohort data) and AML (6 and 9 cases, respectively); the number of exposed cases was smaller for the other leukemia subtypes.

Overall effect of exposure

A minor and statistically nonsignificant decrease was observed for the risk of adult leukemia by cumulative exposure to residential magnetic fields of power lines (table 18). The RR per 1 μT-year was 0.93 in the cohort study and 0.86 in the case-cohort study (both nonsignificant). The highest exposure category of ≥ 2.00 μT-years provided the lowest risk estimate, and the second highest exposure category of 1.00—1.99 μT-years had the second lowest exposure estimate. These results were adjusted for the effects of gender, age, and municipality, and they were not susceptible to change due to adjustment for other covariates because of the removal of

Table 18. Leukemia risk by cumulative exposure to magnetic fields. (O = observed number of leukemia cases, E = expected number of leukemia cases, SIR = standardized incidence ratio, 95% CI = confidence interval, IRR = incidence rate ratio)

Cumulative exposure	Cohort						Case-cohort			
	O	E[a]	SIR[b]	95% CI	IRR[c]	95% CI	Cases	Referents	OR[b]	95% CI
Polytomous exposure										
< 0.20 μT-years[d]	.	.	.	.	.	.	143	1405	1.00	.
0.20—0.39 μT-years	.	.	.	.	.	.	23	261	0.88	0.56—1.39
< 0.40 μT-years	179	185.2	0.97	0.83—1.12	1.00	.	.	.	.	.
0.40—0.99 μT-years	15	17.4	0.86	0.48—1.42	0.88	0.52—1.49	21	181	1.12	0.69—1.81
1.00—1.99 μT-years	5	6.3	0.80	0.26—1.86	0.82	0.34—1.98	5	59	0.86	0.34—2.21
≥ 2.00 μT-years	4	5.7	0.70	0.19—1.79	0.72	0.27—1.95	4	52	0.77	0.28—2.17
Dichotomous exposure										
≥ 0.20 μT-years							53	553	0.42	0.06—3.11
≥ 0.40 μT-years	24	29.4	0.82	0.52—1.21	0.84	0.55—1.28	30	292	1.3	0.68—1.55
≥ 1.00 μT-years	9	12.0	0.75	0.34—1.43	0.78	0.40—1.52	9	111	0.82	0.41—1.67
≥ 2.00 μT-years	4	5.7	0.70	0.19—1.79	0.74	0.27—1.98	4	52	0.78	0.28—2.19
Continuous exposure										
per 1 μT-year	203	214.6	.	.	0.93	0.76—1.13	196	1958	0.86	0.67—1.11

[a] Based on corresponding gender-, age- and calendar year-specific incidence rates in Finland.
[b] Matched odds ratio, adjusted for type of municipality.
[c] Adjusted for gender, age (5-year age groups), and type of municipality.
[d] The cut-off point of 0.20 μT-years was used in the case-cohort analyses but not in the cohort setting.

some influential data points or the selection of another risk model. A description of the selection of the multiplicative model with the best fit, the assessment of the fit of this model, and the alternative risk models follows.

Multiplicative model with best fit. The fitting of a hierarchy of model equations with polytomous variables for cumulative exposure showed that the terms for gender, age, and municipality should be included also in the final model because the P-values of the likelihood ratio tests relating to the stepwise addition of the respective main effect terms in the cohort analyses, and to the addition of the term for municipality in the case-cohort analyses, were all statistically significant (appendix 3, tables 1 and 2). When a set of analogous models were fitted with a continuous estimate for exposure, the deviances turned out to be practically identical to the previous ones, and the conclusions drawn from the significance tests remained untouched. The addition of the terms for cumulative exposure was nonsignificant in all cases.

The plot of deviance residuals versus fitted values showed no obvious trend or pattern in the data. The plot of the hat matrices versus record index numbers revealed the existence of 25 data points (out of the total of 2222 records) with a large influence on model fit. All such cells were with a reference exposure of < 0.40 μT-years and had fit values greater than the observed values. The elimination of these data points did not, however, change the risk estimates for cumulative exposure.

Other models of risk. Various multiplicative and additive models (see the section on the statistical methods on page 27) were fit to the cohort and case-cohort data. Exposure was treated both as polytomous and continuous. The deviances of the first five models using cohort data were within the range of 499.0 to 499.2 (see the model definitions in appendix 3, table 3; the actual numbers are not shown), indicating no difference in the fit among the relative risk models.

These same models were also fit with a continuous variable for age because the additive models using a polytomous variable for age did not converge. The new deviances were from 519.2—519.4 of the relative risk models to 519.7 of the additive model; thus no difference in the fit was indicated between the relative risk and the additive models (appendix 3, table 3). When the case-cohort data were used, only the multiplicative models (appendix 3, table 4) converged, yielding the corresponding deviances of 933.4, 932.5, and 931.0.

The same series of models was also fit for modeling the numbers of observed and expected cases of leukemia (the expected numbers based on Finnish national rates). The relative risk estimates and related 95% CI values for cumulative exposure were changed by less than 0.02 percentage units.

When leukemia risk was studied by continuous cumulative exposure in the specific covariate categories, no statistically significant increases in risk were observed (table 19). Restriction to the subjects without occupational exposure to magnetic fields did not essentially change the estimates of leukemia risk from exposure to magnetic fields of power lines.

No increase was observed in the OR values for the highest annual average magnetic field (table 20), the OR per 1 μT being 0.55 (95% CI 0.14—2.13).

Dependence of dose-response on time

The dependence of dose-response on time was assessed by calculating the leukemia OR values using each of the annual average magnetic fields. The zero time was set at the calendar year of diagnosis. The adjusted OR values were calculated for each year of exposure in relation to zero time, beginning from the year 20 before diagnosis until the year before diagnosis. These adjusted OR values have been plotted in figure 7 using the continuous estimate for magnetic fields. The OR values were be-

Table 19. Leukemia risk by continuous cumulative exposure (μT-years) in the various covariate categories. (IRR = incidence rate ratio, 95% CI = confidence interval, OR = odds ratio)

Variable	IRR[a]	95% CI	OR[b]	95% CI
Gender				
Men	0.83	0.59—1.17	0.81	0.55—1.21
Women	1.00	0.79—1.27	0.91	0.66—1.25
Age				
20—34 years	0.76	0.19—2.99	1.01	0.41—2.46
35—49 years	0.44	0.07—2.61	0.18	0.02—1.58
50—64 years	0.95	0.63—1.42	0.90	0.57—1.41
≥ 65 years	0.97	0.77—1.22	0.91	0.69—1.20
Calendar period of observation				
1974—1981	0.90	0.57—1.40	0.86	0.50—1.46
1982—1989	0.94	0.76—1.17	0.86	0.65—1.14
Municipality				
Urban	0.84	0.64—1.11	0.88	0.64—1.21
Rural	1.11	0.83—1.47	0.84	0.57—1.24
Social class[c]				
I or II	0.90	0.61—1.33	1.23	0.53—2.86
III or IV	0.93	0.74—1.18	0.71	0.46—1.10
Education				
Primary or less	0.98	0.81—1.19	0.90	0.70—1.14
Secondary or more	0.12	0.004—3.32	0.36	0.034—3.86
Marital status				
Unmarried	0.85	0.43—1.68	0.86	0.37—1.97
Married	0.91	0.72—1.16	0.84	0.61—1.15
Divorced	no usable data		no usable data	
Widowed	1.08	0.74—1.56	1.08	0.68—1.71
Occupational exposure to magnetic fields				
Not exposed	0.91	0.72—1.15	0.83	0.53—1.32
Possibly or probably exposed	0.98	0.67—1.42	no usable data	
Type of housing				
House	0.84	0.63—1.13	0.61	0.35—1.05
Other	1.04	0.80—1.35	1.13	0.72—1.77

[a] Adjusted for gender, age, and type of municipality.
[b] Matched odds ratio, adjusted for type of municipality.
[c] See page 24 for an explanation of the classes.

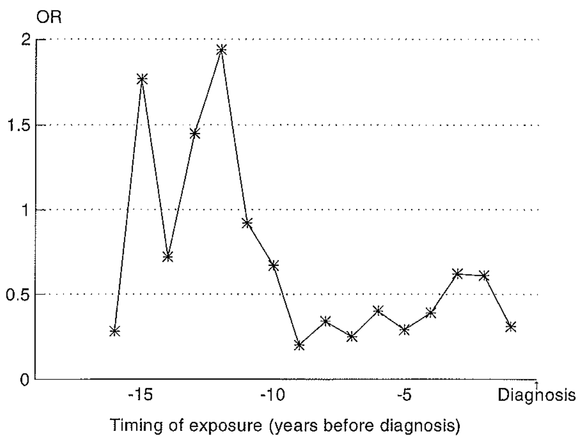

Figure 7. Leukemia risk by magnetic field exposure relative to year of diagnosis. Odds ratio (OR) of leukemia per 1 μT-year increase in exposure versus time of magnetic field exposure (ie, versus number of years before diagnosis).

Table 20. Leukemia risk by highest annual average exposure to magnetic fields. (OR = odds ratio, 95% CI = 95% confidence interval)

Highest exposure	Case-cohort			
	Cases	Referents	OR[a]	95% CI
Polytomous exposure				
< 0.10 μT	176	1751	1.00	·
0.10—0.19 μT	13	115	1.10	0.60—1.99
0.20—0.29 μT	4	35	1.15	0.40—3.33
≥ 0.30 μT	3	57	0.53	0.16—1.70
Dichotomous exposure				
≥ 0.10 μT	20	207	0.95	0.59—1.54
≥ 0.20 μT	7	92	0.76	0.35—1.66
≥ 0.30 μT	3	57	0.52	0.16—1.69
Continuous exposure				
per 1 μT	196	1958	0.55	0.14—2.13

[a] Matched odds ratio, adjusted for type of municipality.

low 1 (all nonsignificant) with the exception of somewhat elevated OR values for the years 15, 13, and 12 before diagnosis (1.77, 1.45, and 1.94, respectively).

Induction time

The results of the analysis using time since first exposure to magnetic fields of ≥ 0.10 μT suggest a slight risk increase for exposures which began three or more years earlier (table 21). The OR values for the exposure categories of <3 (reference), 3—5, 6—8, 9—11, and ≥ 12 years before diagnosis were 1.00 (reference), 2.10, 1.48, 1.20, and 1.86; this analysis was based on 20 cases.

Cumulative exposures were calculated for the three exposure periods of 0—4 years, 5—9 years, and ≥ 10 years before diagnosis. The leukemia OR values were, respectively, 0.98, 0.85, and 1.88 with a cumulative exposure of ≥ 0.40 μT-years (all nonsignificant) (table 22). The risk estimates with continuous cumulative exposure

Table 21. Leukemia risk by time since first exposure to magnetic fields of ≥ 0.10 μT. (OR = odds ratio, 95% CI = 95% confidence interval)

Time since first exposure	Cases	Referents	OR[a]	95% CI
Polytomous exposure				
< 3 years	2	33	1.00	·
3—5 years	7	54	2.10	0.41—10.7
6—8 years	4	45	1.48	0.25—8.62
9—11 years	2	28	1.20	0.16—9.05
≥ 12 years	5	47	1.86	0.34—10.2
Dichotomous exposure				
≥ 3 years	18	174	1.73	0.38—7.84
≥ 6 years	11	120	0.92	0.36—2.34
≥ 9 years	7	75	0.99	0.38—2.59
≥ 12 years	5	47	1.20	0.41—3.48
Continuous exposure				
per 1 year	20	207	1.01	0.92—1.10

[a] Matched odds ratio, adjusted for type of municipality.

Table 22. Leukemia risk by cumulative exposure and timing of exposure with respect to diagnosis. (OR = odds ratio, 95% CI = 95% confidence interval)

Cumulative exposure	Timing of cumulative exposure											
	< 5 years before diagnosis				5—9 years before diagnosis				≥ 10 years before diagnosis			
	Cases	Referents	OR[a]	95% CI	Cases	Referents	OR[a]	95% CI	Cases	Referents	OR[a]	95% CI
Dichotomous exposure[b]												
≥ 0.20 μT-years	28	309	0.89	0.58—1.35	21	209	1.19	0.71—1.97	13	118	1.39	0.70—2.77
≥ 0.40 μT-years	14	142	0.98	0.55—1.72	7	96	0.85	0.38—1.92	8	56	1.88	0.79—4.49
Continuous exposure												
per 1 μT-year	196	1958	0.76	0.46—1.24	130	1421	0.70	0.33—1.48	69	762	0.95	0.47—1.90

[a] Matched odds ratio, adjusted for type of municipality.
[b] Risk estimates relating to polytomous exposure or to dichotomous exposures with cut-off points of 1.00 and 2.00 μT-years are not reported because of the small numbers.

were all below unity. These findings point to a long induction period rather than to a short one.

Effect of exposure duration

Practically no risk increase was observed for duration of exposure to magnetic fields of ≥ 0.10 μT; only the OR for the longest duration (≥ 12 years) was slightly increased (OR 1.53) (table 23). No risk increase by duration of exposure was observed within the higher exposure category of ≥ 0.20 μT either, the OR per 1 μT being 0.89 (95% CI 0.77—1.02).

Reversibility of the effect

The possibility of leukemia risk decreasing after exposure to the magnetic fields of power lines ceases was also studied. The OR per year of time since last exposure to magnetic fields of ≥ 0.10 μT was 1.08 (95% CI 0.94—1.25); the OR values with the dichotomous cut-off points of 3, 6, and 9 years of time since last exposure were 1.34, 2.08, and 2.62, respectively (table 24). The number of cases was too small for an analysis with a polytomous measure for time since last exposure and with a higher dichotomous cut-off point of exposure.

Summary

No risk increase was observed for adult leukemia in relation to overall exposure to magnetic fields of power lines. However, this principal result did not exclude the possibility of a risk increase for a more specific exposure measure or for a leukemia subtype, and it seemed relevant to explore further whether some aspect of leukemogenesis related to magnetic fields would be more probable than its alternatives. The more particular results of the present study found no dose-response for the annual average magnetic field during the 10-year period preceding the diagnosis. However, there was some suggestion — although statistically nonsignificant — that an induction period longer than 10 years might exist and that the effect of magnetic fields on the RR of leukemia in adults might not be reversible. Practically no effect was observed with regard to exposure duration.

Table 23. Leukemia risk by duration of exposure to magnetic fields of ≥ 0.10 μT. (OR = odds ratio, 95% CI = 95% confidence interval)

Duration of exposure	Cases	Referents	OR[a]	95% CI
Polytomous exposure				
< 3 years	185	1751	1.00	.
3—5 years	5	66	1.00	0.46—2.20
6—8 years	1	48	0.27	0.05—1.43
9—11 years	1	58	0.35	0.07—1.87
≥ 12 years	4	35	1.53	0.63—3.73
Dichotomous exposure				
≥ 3 years	11	207	0.77	0.46—1.32
≥ 6 years	6	141	0.65	0.32—1.31
≥ 9 years	5	93	0.92	0.42—2.00
≥ 12 years	4	35	1.57	0.64—3.82
Continuous exposure				
per 1 year	196	1958	0.98	0.93—1.04

[a] Matched odds ratio, adjusted for type of municipality.

Table 24. Leukemia risk by time since last exposure to magnetic fields of ≥ 0.10 μT. (OR = odds ratio, 95% CI = 95% confidence interval)

Time since last exposure	Cases	Referents	OR[a]	95% CI
Dichotomous exposure				
≥ 3 years	7	35	1.34	0.51—3.51
≥ 6 years	4	14	2.08	0.65—6.72
≥ 9 years	2	8	2.62	0.52—13.2
Continuous exposure				
per year	20	207	1.08	0.94—1.25

[a] Matched for odds ratio, adjusted for type of municipality.

Risk of chronic lymphatic leukemia

Overall effect of exposure

Most of the relative risk estimates for CLL with overall exposure were, contrary to those for total leukemia,

Table 25. Risk of chronic lymphatic leukemia by cumulative exposure. (O = observed number of leukemia cases, E = expected number of leukemia cases, SIR = standardized incidence ratio, 95% CI = 95% confidence interval, IRR = incidence rate ratio, OR = odds ratio)

Cumulative exposure	Cohort						Case-cohort		
	O	E[a]	SIR	95% CI	IRR[b]	95% CI	Cases	OR[c]	95% CI
Polytomous exposure									
< 0.20 μT-years[d]	.	.	.	.	.	.	50	1.00	.
0.20—0.39 μT-years	.	.	.	.	.	.	9	0.95	0.45—2.00
< 0.40 μT-years	60	60.0	1.00	0.76—1.29	1.00	.	.	.	.
0.40—0.99 μT-years	6	6.0	1.00	0.37—2.17	0.96	0.42—2.23	8	0.98	0.45—2.15
1.00—1.99 μT-years	3	2.2	1.39	0.29—4.06	1.35	0.42—4.29	3	1.29	0.37—4.43
≥ 2.00 μT-years	3	2.1	1.46	0.30—4.26	1.40	0.44—4.56	3	1.66	0.48—5.78
Dichotomous exposure									
≥ 0.20 μT-years	.	.	.	.	.	.	23	1.01	0.13—7.99
≥ 0.40 μT-years	12	10.2	1.17	0.61—2.05	1.13	0.61—2.10	14	1.15	0.62—2.12
≥ 1.00 μT-years	6	4.2	1.42	0.52—3.09	1.38	0.60—3.17	6	1.46	0.60—3.59
≥ 2.00 μT-years	3	2.1	1.46	0.30—4.26	1.39	0.44—4.41	3	1.65	0.48—5.68
Continuous exposure									
per 1 μT-year	72	70.2	.	.	1.08	0.86—1.35	73	0.96	0.72—1.28

[a] Based on corresponding gender-, age- (5-year age groups), and calendar year-specific incidence rates in Finland.
[b] Adjusted for gender, age, and type of municipality.
[c] Matched odds ratio, adjusted for type of municipality.
[d] Cut-off point of 0.20 μT-years was used in the case-cohort analyses but not in the cohort setting.

somewhat elevated but the 95% CI values included the RR of unity (table 25). The relative risk estimates, obtained using the three analytical approaches, were within the following ranges for the four successive exposure categories: <0.40 μT-years: 1.00 (reference); 0.40—0.99 μT-years: 0.96—1.00; 1.00—1.99 μT-years: 1.29—1.39; and ≥ 2.00 μT-years: 1.40—1.66.

The RR with continuous cumulative exposure (per 1 μT-year) was within the range of 0.96—1.08. The various means of adjustment did not have an essential effect on the estimates of RR.

No risk increase was observed for CLL in association with the highest magnetic field ever (table 26).

Dependence of dose-response on time

The results from the analyses restricted to three mutually exclusive exposure periods (ie, 0—4 years, 5—9 years, and ≥ 10 years before diagnosis) suggested that some risk increase in CLL may have been related to the earlier exposures. The OR values corresponding to the three exposure periods were 0.81 (95% CI 0.34—1.93), 1.42 (95% CI 0.57—3.56), and 3.23 (95% CI 0.91—11.45) for the highest average magnetic field of ≥ 0.10 μT (not shown in the tables); a higher cut-off point for exposure could not be used due to the small numbers.

Table 26. Risk of chronic lymphatic leukemia by the highest annual average exposure to magnetic fields. (OR = odds ratio, 95% CI = 95% confidence interval)

Highest exposure	Cases	OR[a]	95% CI
Polytomous exposure			
< 0.10 μT	65	1.00	.
0.10—0.19 μT	5	0.96	0.37—2.48
0.20—0.29 μT	1	1.37	0.16—11.4
≥ 0.30 μT	2	0.87	0.20—3.79
Dichotomous exposure			
≥ 0.10 μT	8	0.97	0.45—2.10
≥ 0.20 μT	3	0.99	0.30—3.32
≥ 0.30 μT	2	0.87	0.20—3.79
Continuous exposure			
per 1 μT	73	0.51	0.05—5.50

[a] Matched for odds ratio, adjusted for type of municipality.

Induction time

An excess risk of CLL was associated with older magnetic field exposures; the OR values were 0.84, 1.44, and 4.62 for cumulative exposures for 0—4, 5—9, and ≥ 10 years before the diagnosis (table 27). The corresponding OR values for continuous cumulative exposure were 0.82, 0.87, and 1.84 per 1 μT-year (all nonsignificant). A comparative series of OR values could not be given with a higher dichotomous cut-off point due to the small numbers for the exposure periods of 5—9 and ≥ 10 years.

The RR for CLL declined as age increased at first exposure to magnetic fields of ≥ 0.10 μT although the 95% CI values included the RR of unity. The OR values for the age groups of 35—49, 50—64, and ≥ 65 years were 2.23 (95% CI 0.14—36.3), 1.30 (95% CI 0.22—7.57), and 1.00 (reference); no exposed cases were observed in the age group of <35 years (not shown in the tables).

Effect of exposure duration

An almost fivefold increase in the OR of CLL was observed for those having lived in a magnetic field of ≥ 0.10 μT for 12 or more years (OR 4.80) but not for those with a shorter duration of such exposure (table 28).

The effect of cut-off point selection was studied by fitting a linear model with the OR values obtained with

Table 27. Risk of chronic lymphatic leukemia by cumulative exposure and exposure period with respect to diagnosis. (OR = odds ratio, 95% CI = 95% confidence interval)

Cumulative exposure	Timing of cumulative exposure								
	< 5 years before diagnosis			5—9 years before diagnosis			≥ 10 years before diagnosis		
	Cases	OR[a]	95% CI	Cases	OR[a]	95% CI	Cases	OR[a]	95% CI
Dichotomous exposure[b]									
≥ 0.20 μT-years	12	0.93	0.48—1.78	11	1.48	0.72—3.05	9	2.79	1.06—7.37
≥ 0.40 μT-years	5	0.84	0.32—2.15	5	1.44	0.52—3.96	6	4.62	1.41—15.1
Continuous exposure									
per 1 μT-year	73	0.82	0.42—1.61	53	0.87	0.38—2.02	30	1.84	0.70—4.82

[a] Matched odds ratio, adjusted for type of municipality.
[b] Risk estimates relating to polytomous exposure or to dichotomous exposures with cut-off points of 1.00 and 2.00 μT-years are not reported because of the small numbers.

Table 28. Risk of chronic lymphatic leukemia by duration of exposure to magnetic fields of ≥ 0.10 μT. (OR = odds ratio, 95% CI = 95% confidence interval)

Duration of exposure	Cases	OR[a]	95% CI
Polytomous exposure			
< 3 years	67	1.00	.
3—5 years	1	0.54	0.10—3.01
6—8 years	1	0.55	0.10—3.00
9—11 years	1	0.81	0.15—4.50
≥ 12 years	3	4.80	1.52—15.2
Dichotomous exposure			
≥ 3 years	6	1.10	0.53—2.65
≥ 6 years	5	1.37	0.62—3.04
≥ 9 years	4	2.17	0.86—5.43
≥ 12 years	3	4.86	1.54—15.4
Continuous exposure			
per 1 year	73	1.03	0.96—1.11

[a] Matched odds ratio, adjusted for type of municipality.

various dichotomous cut-off points of exposure duration (1 through 20 years) (figure 8). A 12% increase in the OR was observed for the addition of one year to the dichotomous cut-off point for exposure duration (P = 0.02).

Reversibility of the effect

The OR of CLL was higher for the subjects with ≥ 3 years of time since exposure to magnetic fields of ≥ 0.10 μT than in the reference category (OR 1.41) (table 29). The OR values corresponding to the dichotomous cut-off points of six years and nine years were 2.57 and 2.62, respectively. A model with a polytomous exposure estimate could not be fitted due to the small numbers.

Summary

Contrary to the case for all forms of leukemia combined, most of the risk estimates for CLL were somewhat elevated, but generally the risk increases were not statistically significant. The two exceptions were exposures of ≥ 10 years before the diagnosis and ≥ 12 years of duration, both being associated with an almost fivefold increase in the RR of CLL. The first risk estimate was based on six exposed cases and the latter on three exposed cases. None of the exposed cases were recognized as "exposed" by the other exposure estimate. A nonsignificant, threefold increase in the risk for CLL was ob-

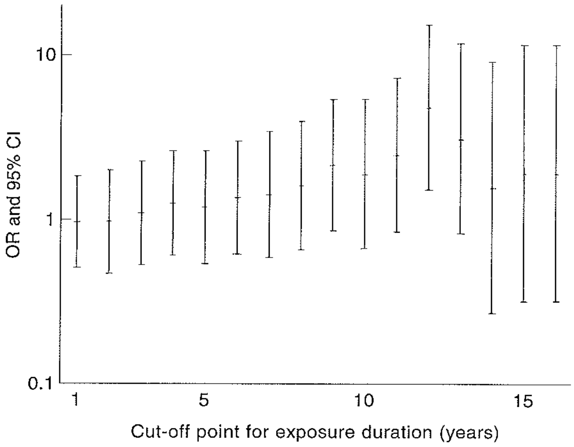

Figure 8. Dependence of the risk of chronic lymphatic leukemia on the selection of the cut-off point for exposure duration. The odds ratios (OR) and 95% confidence intervals (95% CI) are for chronic lymphatic leukemia by exposure duration greater than the cut-off point (years) versus exposure duration shorter than the cut-off point.

Table 29. Risk of chronic lymphatic leukemia by time since last exposure to magnetic fields of ≥ 0.10 μT. (OR = odds ratio, 95% CI = 95% confidence interval)

Time since last exposure	Cases	OR[a]	95% CI
Dichotomous exposure			
≥ 3 years	3	1.41	0.32—6.34
≥ 6 years	2	2.57	0.46—14.4
≥ 9 years	1	2.62	0.26—26.7
Continuous exposure			
per 1 year	8	1.07	0.85—1.35

[a] Matched odds ratio, adjusted for type of municipality.

served for magnetic fields of ≥ 0.10 μT in the exposure period of ≥ 10 years before the diagnosis.

Risk of other types of leukemia

Overall, no increased risks were observed for AML, ALL or other types of leukemia. The SIR for cumulative exposure of ≥ 0.40 μT-years was 0.65 for AML (based on 6 exposed cases), 1.03 for ALL (based on 2 exposed cases), and 0.50 for the other types (based on 4 exposed cases); all the 95% CI values included the SIR of 1.00 (table 30).

The RR values of AML for a cumulative exposure of ≥ 0.40 μT-years were close to unity also in the IRR analysis (6 exposed cases, IRR 0.69, 95% CI 0.30—1.60) and in the case-cohort analysis (9 exposed cases, OR 1.21, 95% CI 0.47—2.55). The results of the leukemia subtype analyses, other than the SIR one, are presented in appendix 4.

Table 30. Observed (O) and expected (E) numbers of leukemia, standardized incidence ratios (SIR), and 95% confidence intervals (95% CI) for acute myeloid leukemia, acute lymphatic leukemia, and types other than chronic lymphatic leukemia, acute myeloid leukemia and acute lymphatic leukemia, by cumulative exposure in the cohort data.

Cumulative exposure	Acute myeloid leukemia				Acute lymphatic leukemia				Other leukemia			
	O	E[a]	SIR	95% CI	O	E[a]	SIR	95% CI	O	E[a]	SIR	95% CI
Polytomous exposure												
< 0.40 μT-years	58	78.3	0.74	0.56—0.96	10	14.4	0.70	0.33—1.28	51	51.1	1.00	0.74—1.31
0.40—0.99 μT-years	6	5.5	1.09	0.40—2.38	1	1.2	0.86	0.02—4.76	2	4.8	0.42	0.05—1.52
1.00—1.99 μT-years	—	2.0	0	0—1.86	1	0.4	2.38	0.06—13.3	1	1.7	0.58	0.02—3.26
≥ 2.00 μT-years	—	1.8	0	0—2.10	—	0.4	0	0—10.5	1	1.6	0.65	0.02—3.59
Dichotomous exposure												
≥ 0.40 μT-years	6	9.2	0.65	0.24—1.42	2	1.9	1.03	0.13—3.72	4	8.0	0.50	0.14—1.28
≥ 1.00 μT-years	—	3.7	0	0—0.99	1	0.8	1.30	0.03—7.24	2	3.3	0.61	0.07—2.22
≥ 2.00 μT-years	—	1.8	0	0—2.10	—	0.4	0	0—10.5	1	1.6	0.65	0.02—3.59

[a] Based on corresponding gender-, age- (5-year age groups), and calendar year-specific incidence rates in Finland.

Discussion

Material and methods

Material

Coverage of the study cohort. The data collection of this study sought to include all Finnish people having lived any period of time in 1970—1989 within a distance of 500 m of 110, 220, and 400 kV power lines in a magnetic field of ≥ 0.01 μT. The data sources generally provided a good coverage although some persons meeting the entrance criteria of the study cohort probably remained unidentified:

1. Data on approximately 91% of the total length of power lines in Finland was accessible for study. The power lines with missing data were owned by local power companies.
2. The register of buildings and individual premises in the Central Population Register included computerized data on all contemporary buildings existing at the time of the record linkage (1990). Buildings that had been torn down, or otherwise destroyed, could not be identified.
3. Residential histories were complete for the years between 1984 and 1989; in addition, the two latest addresses were obtained from the personal data files of the Central Population Register. In cases of more frequent movers, the earlier parts of the individual residential histories were lost.
4. Subjects deceased before 1974 could not be identified with certainty from the active person data files of the Central Population Register.
5. The undercoverage of the population census in 1970 has been estimated to be about 30 000 people (or 0.7% of the total population of 4.6 million in 1970) (139). The response rate for different questions varied around 90%. The answers of 2800 people in the population census were later compared with an independent household inquiry made in 1970—1971. The agreement was 98% for marital status, 95% for education, 88% for occupation, and 91% for housing type.

The exact number of people lost cannot be exactly assessed solely on the basis of the collected data. The preceding item 1 roughly suggests a coverage of 90% for the study cohort, presuming the housing density along the lost power lines corresponded to that along the identified power lines. This figure may be slightly lower because most of the lost power lines were 110 kV lines, which are usually situated in urban areas. Items 2 and 3 also somewhat decreased the figure of 90%. A decision of not including those having died before 1974 was made to deal with item 4. As to item 5, the population census of 1970 appears to be a reliable source of covariate information. The described undercoverage led unavoidably into misclassifying some of the subjects with actual exposure to magnetic fields of power lines as being "unexposed" but not vice versa. The effect would be to bias slightly the observed RR estimates towards unity.

Completeness of leukemia registration in Finland. In one Finnish study (140), published in 1994, the completeness of cancer registration was investigated for the years 1985—1988 by comparing the files of the Finnish Cancer Registry with the hospital discharge register. The latter covers all patients who have been admitted to a hospital in Finland and includes dates of hospitalization and main diagnoses. Cancer diagnoses that were found solely in the hospital discharge register were checked on the basis of original patient records. The observed underregistration rate was 0.9% for solid tumors and 7.9% for hematological cancers in general. As to leukemia subtypes, it was 4.2% for acute leukemia and as high as 24.7% for other forms of leukemia. However, this underregistration was at least partly corrected by late registrations through death certificates. Furthermore, the underregistration was corrected for the years 1985—1988, which improved the coverage of the present study, too. If it is assumed that the underregistration rates were 4% for acute and 25% for chronic leukemia during 1974—1984 and 1989—1990, it can be estimated that the present study failed to identify two cases of acute leukemia (58 observed cases; 58/0.96—58) and 32 cases of chronic leukemia (97 observed cases; 97/0.75—97).

The accuracy of the primary tumor site is generally considered good (some 2% of all cancers were coded to "primary site unknown" in the early 1990s) although some problems may arise in the differentiation between CLL and lymphoma. The date of diagnosis is judged to have given no major problems in epidemiologic studies although the delay in reporting a CLL diagnosis to the Finnish Cancer Registry was more than three years in some 10% of the cases (7 out of 73) of the present study.

Exposure assessment

Most fundamentally, the truly leukemogenic exposure to magnetic fields — if any — has not been recognized, and it is unclear to what extent the annual average magnetic field approximates the truly leukemogenic exposure. However, there is no reason to accept the opposite either (ie, that the average would not be a relevant surrogate measure).

Some degree of misclassification of overall exposure was unavoidable since power lines are only one of several magnetic field sources. For instance, occupational field sources may, in some cases, be entirely dominant when compared with power lines. (See the section on residential and occupational magnetic fields on page 6.) On the other hand, there is also the possibility of exposure to magnetic fields from other residential magnetic field sources such as transformers, indoor electrical wiring, and the whole variety of electric appliances. (See appendix 1.)

The reliability of the calculated 50-Hz magnetic fields as a measure of annual *average exposure* depends on the base-line data and on the magnetic field calculations. The relating measurement error questions have been thoroughly addressed in some previous publications (129, 130, 141) and will be summarized in this context only briefly.

Of the power-line related factors, harmonics and unbalanced currents were not taken into account in the actual calculation of magnetic field estimates. According to some previous publications (129, 130, 141), harmonics are hardly remarkable when the line is in normal operation, although they do complicate the view of magnetic field exposure. Likewise, the unbalanced currents were not considered to be very important due to the small imbalance of the Finnish transmission grid.

The point estimate of load current, used for the field calculations, has previously been shown to be a reasonable surrogate for the actual annual average load current. The effect of distance error on the calculated magnetic field was large in the immediate vicinity of a power line but diminished to an acceptable magnitude at some distance away from the line. The effects of errors in tower type and in the height of conductors have also been estimated earlier.

Calculated magnetic field is a rather theoretical quantity without an explicit correspondent in reality. In this study, it was assumed that a calculated magnetic field smaller than 0.1 μT would have no effect on the hypothetical background level of 0.1 μT; the lowest dichotomous cut-off point for a calculated magnetic field was set at 0.10 μT. The calculated magnetic field estimates are, however, annual averages, and therefore even these low levels of calculated magnetic fields have probably added somewhat to the typical background field for some duration of time. Anyhow, the exposure level within the exposed group was low in comparison with levels that occur commonly in occupational environments; in other words, one could not expect to observe a dramatic increase in the risk of leukemia.

In short, it appears reasonable to assume that the overall exposure misclassification resulting from all these sources was random in nature and has had an overall effect of biasing the observed RR towards unity. Further statistical evaluation of these problems was not possible with the traditional approaches used in the present study; some of the emerging approaches and newly developed computer programs such as Markov-Chain-Monte-Carlo estimation (142) with *Bugs* software (143), might, however, provide a tool for directly assessing the effect of exposure misclassification on the actual risk estimates.

Presence of confounding

Although the causes of leukemia are largely unknown, there are some environmental factors such as chemicals, ionizing radiation, and smoking that may play a role in leukemogenesis. Some chromosome disorders and therapeutic drugs have also been shown to be of importance. In this register-based study, indirect measures for potentially confounding determinants had to be relied upon instead of more direct means. The possibility of confounding by gender, age, calendar period, municipality, social class, marital status, education, occupation, and type of housing was considered in the statistical analysis of the present study.

Gender and age were important and statistically significant confounders in this study, and the results were adjusted for their effects.

Smoking is a potential confounder in studies on magnetic fields of power lines and adult leukemia. Since no direct measures for smoking were available, its effect had to be estimated by using more indirect measures. Smoking is described to be unequally distributed by social class and marital status (144), which can be interpreted to be surrogates of smoking. Adjusting for social class or marital status did not change the risk estimates for leukemia and therefore suggested that the results of the present study were not essentially confounded by smoking.

Chemical-related leukemia cases have been estimated to be less than 1% of the total (73) and are thus unlikely to have introduced important confounding into this study. Although a recent Finnish study (68) found slightly elevated leukemia risks among some occupations possibly associated with benzene exposure, the present study did not adjust for occupational exposure to leukemogenic chemicals. Anyhow, there is no obvious reason why any occupational exposure with a leukemogenic effect would be associated with residential magnetic fields of power lines and thus confound the results.

The traffic density in the vicinity of residences was not measured directly. On the other hand, the type of municipality had a minor but statistically significant effect on the results (higher risk in urban environment). It is unclear whether this could be explained to some extent by the exhaust gases (and benzene) in urban air.

The possibility of confounding by chemotherapeutic drugs with a leukemogenic side effect was considered by restricting the case-cohort analyses to the subjects with no malignant tumors prior to the date of leukemia diagnosis. This procedure did not essentially alter the results.

In short, confounding by gender, age, and municipality were controlled for in the statistical analyses of the present study. The possibility of confounding by smoking was considered using some indirect measures, but it was assessed to be either minimal or nonexisting. However, it is obvious that some residual confounding may have remained.

Power of the study

All the power-line studies share the problem of small numbers. The number of exposed cases in the present study was between 20 and 30, depending on the exposure measure, and thus was of the same magnitude as the number of exposed cases in the earlier studies by Wertheimer & Leeper (26), Severson et al (32) and Feychting & Ahlbom (24). The other three studies on magnetic fields of power lines and adult hematological malignancies each had fewer than 10 exposed cases (19, 21, 22).

In principle, the present study could have detected (SIR analysis, $\alpha = 0.05$, power = 0.80) a 70% increase in leukemia risk for persons with a cumulative exposure of ≥ 1.00 μT-years or a 100% increase for those with a cumulative exposure of ≥ 2.00 μT-years.

Results

No increase in the risk of total leukemia was observed for adults in relation to exposure to 50-Hz magnetic fields of high-voltage power lines. However, there is some uncertainty about the effect of earlier exposures and about the risk of CLL. It appears that the results were not confounded by any of the known leukemogenic agents. Exposure misclassification has probably decreased the possibility of observing an excess leukemia risk.

How do the results of previous studies agree with those obtained in the present investigation? There are four previously published studies on magnetic fields of power lines and total leukemia in adults (19, 21, 25, 26). Two of these studies found RR values of unity (19, 26), whereas, in the other two, weak increases were observed in the risk of total leukemia (21, 25), one being of borderline significance (25) and the other being statistically nonsignificant (21). The study of Youngson et al (22) on hematological malignancies showed somewhat elevated risk estimates, for example, an OR of 1.87 (95% CI 0.79—4.42) for magnetic fields of ≥ 0.3 μT.

The results of the present study are similar to those of previous power-line studies in indicating that no major increase in the risk of adult leukemia is associated with magnetic fields of power lines; moreover, the current results add materially to the credibility of this prior view because of the special strengths of the study (ie, nationwide study base and personal long-time exposure histories). In comparison with the earlier cohort study by McDowall (19), the present study investigated incident cancers (not deceased cases) and had a more than fourfold number of exposed cases. However, the power-line studies are still inconsistent about the existence of a minor-to-moderate increase.

With the assumption of a minor risk increase of 50% and a leukemia incidence rate of 6.0 per 100 000, it can be estimated that about three additional leukemia cases could be expected every year among 100 000 people exposed to magnetic fields at power-line levels. The number of people living near high-voltage power lines is, however, rather small (eg, 15 600 people with a magnetic field of ≥ 0.1 μT in the whole of Finland in 1989), and this fact should be recognized in the evaluation of related public health questions.

The only statistically significant risk increase in the present study was the almost fivefold RR of CLL, both with cumulative exposure restricted to exposures of ≥ 10 years before the diagnosis and with an exposure duration of ≥ 12 years. The risk estimate with the first measure was based on six exposed cases and that with the latter on three (none of the cases was shared by both measures). The results thus suggest that CLL is a possible outcome of interest. The small numbers led to serious limitations with regard to the feasibility of the analyses of other leukemia subtypes. The risk of AML was decreased, which could have been due chance, and conclusions on the relative risks of the other leukemia subtypes cannot be drawn on the basis of this study.

The results of previous studies are inconsistent about the risk of leukemia subtypes although there is some support for CLL being a possible outcome of interest. Feychting & Ahlbom (25) observed a twofold increase in the OR values for AML and CML, whereas the OR for CLL was 1.3. Severson et al (32) found no evidence of an association with wire codes for acute nonlymphatic leukemia; the observed OR being 1.50 (nonsignificant) with the measured magnetic field. Youngson et al (22) observed no trends in myeloid or lymphatic malignancies by distance, but the OR for low-grade lymphatic malignancies was, however, increased twofold in the highest exposure category of ≥0.30 μT. Coleman et al (21) observed a relative risk of 1.76 for ALL and 1.61 for CLL in those living very close to power lines, whereas the relative risks for AML and CML were below unity.

As to occupational studies, a recent Swedish study (41) showed a strong association between CLL and occupational exposure to magnetic fields; another occupational study (44) observed a relative risk of 2.41 (95% CI 1.07—5.44) for acute nonlymphatic leukemia, but there was some evidence for a risk increase in CLL, too.

Perhaps an alternative outcome classification scheme taking advantage of cytogenetic data to subclassify the subjects, as was suggested in the case of leukemia and other environmental factors by Sandler & Collman already in 1987 (145), should be developed also for studies on magnetic fields and leukemia.

As to the more-detailed analyses on possible leukemogenic mechanisms, no evidence was found for dose-response by annual average magnetic field during the 10-year period preceding the diagnosis; neither have the previous epidemiologic studies on residential magnetic fields and adult leukemia found any clear evidence for dose-response. It is possible that such a mechanism does not exist, but it is also possible that dose-response cannot be demonstrated within the narrow range of magnetic fields generated by power lines.

There was some suggestion that an induction period longer than 10 years might be needed and that the effect of magnetic fields might not be reversible. In addition, there was some suggestion that the prolongation of exposure to magnetic fields might increase the risk of CLL. Figure 9 shows that the present study is, as a matter of fact, the only residential study that has investigated the possibility of an induction period longer than 10 years. The base-line exposure data of one other study (25) has covered a comparable exposure period, but no results have been published on the effect of these earlier exposures. On the other hand, a recent Canadian study (44) on occupational magnetic fields calculated cumulative exposures for the three (overlapping) time periods of <5, <20 and ≥20 years before the diagnosis; the association between exposure above the median and

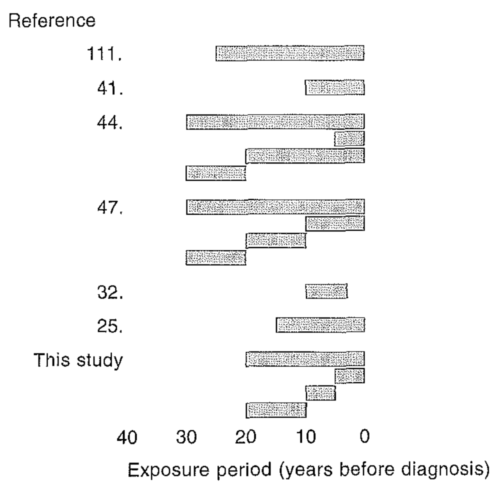

Figure 9. Period of exposure to magnetic fields with respect to time of diagnosis.

AML or acute nonlymphatic leukemia was not apparent for exposure in the five years immediately preceding the diagnosis. As to exposure duration and reversibility of the effect, they have, likewise, been systematically evaluated only in the statistical analyses of the present study.

Concluding remarks

It appears reasonable to assume that no major increase in the risk of adult leukemia is associated with typical residential exposures to magnetic fields of high-voltage power lines. However, there is some uncertainty about the effect of earlier exposures and the risk of chronic lymphatic leukemia. Neither can the possibility of a risk increase at higher magnetic field levels be excluded on the basis of this study. The implementation of this study has clarified the future prospects of evaluating carcinogenesis in relation to electromagnetic fields. It appears essential to investigate higher field levels, and to focus also on time-related factors. Furthermore, the possibility of health effects other than carcinogenesis should be considered. The ubiquitous presence of ELF electromagnetic fields in modern society continues to provide impetus for further clarification of the possible health effects of this man-made environmental agent.

Summary

The objective of this study was to investigate the risk of leukemia in adults exposed to residential 50-Hz magnetic fields generated by high-voltage power lines. The epidemiologic *cohort study* included 383 700 Finnish people living for any period of time during 1970—1989 within 500 m of overhead power lines of 110—400 kV in a magnetic field calculated to be ≥ 0.01 μT. Data collection was based, with the exception of the magnetic field calculations, on several subsequent record linkages of nationwide registers (ie, the Central Population Register, the Finnish cancer register, the population census of 1970). The standardized incidence ratios (SIR) were calculated with 95% confidence intervals (95% CI) using the observed and expected numbers of cancer cases; the incidence rate ratios (IRR) with the 95% CI values were estimated from multiplicative models for leukemia and its subtypes. In the *case-cohort* study, magnetic fields and leukemia were studied in further detail with special emphasis on dose-response and time-related factors.

More than 2.5 million person-years were accumulated by the cohort members after the age of 20 years. A total of 203 leukemia cases occurred within the study cohort during the follow-up. Of them, 64 were acute myeloid leukemias and 12 were acute lymphatic, 72 chronic lymphatic, and 55 of some other type. The incidence rate of leukemia in the whole cohort was 4% lower than that of the general Finnish population.

No increase in the risk of adult leukemia was associated with typical residential exposures to magnetic fields of high-voltage power lines; the IRR for overall leukemia among adults was 0.93 per 1 μT-year (95% CI 0.76—1.13). The statistical analyses using other exposure measures confirmed this principal observation of no increase in the risk of total leukemia. The results were adjusted for gender, age, and municipality, and they did not change due to adjustment for other covariates, or with the selection of another risk model.

There was, however, an almost fivefold increase in the risk of chronic lymphatic leukemia both with exposures received more than 10 years before the diagnosis (6 cases with ≥ 0.40 μT-years received ≥ 10 years before the diagnosis, OR 4.62, 95% CI 1.41—15.1) and with duration of exposure longer than 12 years (3 cases with ≥ 12 years of magnetic field of ≥ 0.1 μT, OR 4.86, 95% CI 1.54—15.4). No increases were observed in the risk of acute myeloid leukemia, acute lymphatic leukemia, and other types of leukemia.

The results suggest that magnetic fields of high-voltage power lines, when occurring at typical residential levels, do not form a major public health risk regarding adult leukemia. The possibility of an increase in the risk of leukemia at higher magnetic field levels, or in relation to old exposures, cannot be eliminated on the basis of this study.

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One morning in April 1988, docent Helena Mussalo-Rauhamaa informed a group of medical students about the possibility of preparing a doctoral dissertation on the issue of power lines and cancer. One of the students — my husband Dr Pekka Nokelainen — told me later that day that he had found the study I had been looking for. Without the help of these two devoted persons, I would never have come to join the Finnish research group on magnetic fields and cancer.

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Helsinki, 23 September 1996
Pia Verkasalo

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Appendices

Appendix 1

Measured magnetic fields of some household electric appliances at a distance of 10, 30, and 50 cm (3)

Electric appliance	Magnetic field (μT)		
	10 cm	30 cm	50 cm
Hand mixer	74	8.7	1.4
Food processor	33	2.8	0.25
Electric drill	16.1	2.1	0.49
Clothes washer (spinning cycle)	11.8	5.5	2.9
Clothes washer (washing cycle)	1.9	0.16	0.08
Vacuum cleaner	10.1	2.5	0.74
Dishwasher	2.8	0.84	0.34
Kitchen range	2.3	0.40	0.14
Electric radiator	2.0	0.19	0.05
Toaster	1.9	0.06	·
Television set	1.4	0.43	0.19
Receiver	1.1	0.24	0.09
Electric typewriter	0.80	0.19	0.09
Heated waterbed	0.73	0.34	0.14
Radio cassette recorder	0.69	0.10	0.04
Hair dryer	0.60	0.08	0.06
Electric sauna stove	0.50	0.24	0.18
Coffee maker	0.47	0.14	0.09
Loudspeaker	0.29	0.20	0.15
Electric iron	0.29	0.06	0.03
Electric toothbrush	0.25	0.05	0.04
Hot brush	0.20	0.08	0.04
Personal computer	0.15	0.09	0.06
Record player	0.14	0.08	0.05
Refrigerator	0.11	0.04	0.03
Electric razor	0.06	0.04	0.03

Appendix 2

Classification of occupational codes from the population census of 1970 according to the likelihood of occupational exposure to extremely low-frequency magnetic fields

Group A. *Occupational codes with possible occupational exposure to extremely low-frequency magnetic fields*

Code	Nomenclature of occupations
004	Mechanical engineers
005	Engineers performing chemotechnical work
006	Engineers performing mining and metallurgical work
013	Mechanical technicians
014	Technicians performing chemotechnical work
015	Technicians performing mining and metallurgical work
031	Dentists
080	Sculptors, painters, etc
081	Commercial artists
088	Radio, television and motion picture producers and editors
140	Book-keeping machine operators
141	Automatic data-processing machine operators
142	Card- and tape-punching machine operators
143	Computing assistants, reproduction machine operators, etc
149	Dispatching and receiving clerks, shipping agents
150	Building caretakers, storeroom clerks
201	Retailers
304	Livestock breeders

311	Garden workers
312	Livestock workers
340	Forestry and floating workers
400	Miners, shot-firers, etc
410	Drilling-machine operators
502	Engine officers
511	Engine-room crew
520	Air plane pilots, flight engineers, etc
530	Locomotive engineers, railway steam engine firemen
550	Railway and station personnel (traffic department)
561	Air traffic controllers
571	Telephone operators (long-distance and local calls)
572	Telephone switchboard operators
573	Telegraphists, radio-communication operators
590	Lighthouse keepers
601	Spinners, etc
602	Weavers
603	Textile machine setter operators
604	Knitters
610	Tailors
611	Dressmakers
616	Sewers, etc (also leather garments and gloves)
622	Shoe sewers
630	Metal smelting furnacemen
631	Heat treaters, hardeners, temperers, etc
632	Hotrollers
633	Coldrollers
639	Other occupations related to this group
640	Precision-instrument makers
642	Opticians
650	Turners, toolmakers and machine-tool setters
651	Fitter-assemblers, etc
652	Machine and motor repairers
654	Plumbers
655	Welders and flame cutters
657	Metal platers and coaters
659	Other occupations related to this group
660	Electricians (indoor installation)
673	Construction carpenters
674	Wooden boatbuilders, coach-body builders
675	Bench carpenters
676	Cabinetmakers, etc
677	Woodworking machine operators, etc
678	Wooden surface finishers
697	Assistant housebuilding workers
698	Other assistant construction workers
701	Printers
710	Glass formers
711	Potters
712	Glass and ceramics kilnmen
720	Grain millers
721	Bakers and pastry makers
722	Chocolate and confectionery makers
723	Brewers, beverage makers and kilnmen
724	Food preservers
725	Butchers and sausage makers
726	Dairy workers
727	Prepared foods makers
728	Sugar processers
729	Other occupations related to this group
730	Distillers
731	Cookers and furnacemen (chemical processes)
732	Crushers, grinders and calender operators (chemical processes)
733	Wood grinders
734	Pulp mill workers
735	Paper and cardboard mill workers
739	Other occupations related to this group
751	Rubber product makers
760	Packers and labelers
770	Crane and hoist operators
771	Truck drivers, etc
773	Operators of stationary engines
810	Housekeeping managers
811	Cooks, etc
812	Kitchen hands
830	Caretakers

Group B. *Occupational codes with probable occupational exposure to extremely low-frequency magnetic fields*

Code	Nomenclature of occupations
002	Engineers performing power-electrical work
003	Engineers performing teletechnicial work
011	Technicians performing power-electrical work
012	Technicians performing teletechnical work
634	Blacksmiths
635	Molders
636	Wire and tube drawers
653	Sheet-metal workers
656	Metal-plate workers and constructional steel erectors
661	Electric machine operators
662	Electric machine fitters
663	Electronics fitters and repairmen (not telephone)
664	Telephone installers and repairmen
665	Linemen and cable jointers
666	Electrical and electronic equipment assemblers
669	Other occupations related to this group (ie, electrical occupations)

Appendix 3

Goodness-of-fit statistics for alternative models of risk

Table 1. Goodness-of-fit statistics (deviances) for a number of multiplicative models fitted to the cohort data. Polytomous cumulative exposure to magnetic fields.

Model	Factors in the model[a]	Degrees of freedom	Deviance	P-value[b]
Grouped data set 1[c]				
1	—	2239	794.7	·
2	CE	2236	794.5	0.98
3	CE + AGE	2223	515.2	0.000
4	CE + AGE + GENDER	2222	503.2	0.001
5	CE + AGE + GENDER + CAL	2221	502.0	0.27
6	CE + AGE + GENDER + MUNFE	2221	499.0	0.04[d]
7	CE + AGE[e] + GENDER + MUNFE	2233	519.2	·
8	CE + AGE[e] + GENDER + MUNFE + CE × AGE[e]	2230	518.5	0.88[f]
9	CE + AGE + GENDER + MUNFE + CE × GENDER	2218	496.1	0.69[f]
10	CE + AGE + GENDER + MUNFE + CE × MUNFE	2218	496.1	0.41[f]
11	CE + AGE + GENDER + MUNFE + SOCLL	2219	497.0	0.37[f]
Grouped data set 2				
12	CE + AGE + GENDER + MUNFE	2221	322.5	·
13	CE + AGE + GENDER + MUNFE + MARITAL	2217	317.1	0.25
Grouped data set 3				
14	CE + AGE + GENDER + MUNFE	1773	294.6	·
15	CE + AGE + GENDER + MUNFE + EDU	1771	292.9	0.44
Grouped data set 4				
16	CE + AGE + GENDER + MUNFE	1325	304.6	·
17	CE + AGE + GENDER + MUNFE + OCCEXP	1324	304.6	0.89
Grouped data set 5				
18	CE + AGE + GENDER + MUNFE	1325	324.1	·
19	CE + AGE + GENDER + MUNFE + RESFE	1324	324.0	0.72

[a] CE = polytomous cumulative exposure; AGE = age at first exposure (5-year age groups); GENDER; CAL = calendar period of observation; MUNFE = type of municipality at first exposure; SOCLL = social class; MARITAL = marital status; EDU = education; OCCEXP = occupational exposure to magnetic fields; RESFE = type of residence at first exposure
[b] Likelihood ratio test with respect to preceding model, unless otherwise noted.
[c] Data sets (see the section on grouped data sets).
[d] Likelihood ratio test with respect to model 4.
[e] AGE, age taken as a continuous variable in order to reduce the number of parameters in the model.
[f] Likelihood ratio test with respect to model 6.

Table 2. Goodness-of-fit statistics (deviances) and score tests for a number of multiplicative models fitted to the case-cohort data. Polytomous cumulative exposure to magnetic fields.

Model	Factors in the model[a]	Free parameters	Deviance	P-value[b]	Score test[c]	P-value[c]
1	—	0	921.9	·	·	·
2	CE + MUNFE + SOCCL + MARITAL + EDU + OCCEXP + RESFE	13	911.9	0.70	9.9	0.70
3	CE	4	920.9	0.93[d]	0.9[e]	0.93[e]
4	CE + MUNFE	5	916.7	0.04	4.1	0.04
5	CE + MUNFE + SOCCL	7	916.5	0.91	0.2	0.92
6	CE + MUNFE + MARITAL	8	914.1	0.46[f]	2.7[g]	0.44[g]
7	CE + MUNFE + EDU	6	916.3	0.53[f]	0.4[g]	0.54[g]
8	CE + MUNFE + OCCEXP	6	916.2	0.50[f]	0.5[g]	0.49[g]
9	CE + MUNFE + RESFE	6	916.4	0.62[f]	0.2[g]	0.62[g]
10	CE + MUNFE + CE × MUNFE	9	908.3	0.08[f]	7.1[g]	0.13[g]

[a] CE = polytomous cumulative exposure to magnetic fields; MUNFE = type of municipality at first exposure; SOCCL = social class; MARITAL = marital status; EDU = education; OCCEXP = occupational exposure to magnetic fields; RESFE = type of residence at first exposure.
[b] Likelihood ratio test with respect to preceding model, unless otherwise noted.
[c] Score statistic and P-value with respect to prededing model, unless otherwise noted.
[d] Likelihood ratio test with respect to model 1.
[e] Score statistic and P-value with respect to model 1.
[f] Likelihood ratio test with respect to model 4.
[g] Score statistic and P-value with respect to model 4.

Table 3. Results of fitting several risk models to the cohort data. Continuous classification of age. (IRR = incidence rate ratio, ER = excess risk)

Model	Equation for relative risk[a] (IRR for the case-cohort data) or excess risk[a] as a function of cumulative exposure (x)	Degrees of freedom	Deviance	Exposure (μT-years)	Parameter estimate	Standard error	T-statistic
Multiplicative models							
1	Separate IRR each category of cumulative exposure	2233	519.2	0.40—0.99	−0.1289	0.2691	−0.48
				1.00—1.99	−0.2061	0.4536	−0.45
				≥ 2.00	−0.3250	0.5060	−0.64
2	$IRR = \exp(\beta x)$	2235	519.4	All	−0.07769	0.1000	−0.78
3	$IRR = \exp(\beta x + \gamma x^2)$	2234	519.2	All	−0.2244	0.3810	−0.59(β)
					0.03114	0.07770	0.40(γ)
Additive relative risk models							
4	$IRR = 1 + \geq x$	2235	519.4	All	−0.06225	0.06967	−0.89
5	$IRR = 1 + \beta x + \gamma x^2$	2234	519.2	All	−0.2004	0.3073	−0.65(β)
					0.02849	0.06232	0.46(γ)
Additive models							
6	Separate ER each dose group	2232	519.5	All		no convergence	
7	$ER = \beta x$	2235	519.7	All	-1.247^{-6}	7.730^{-7}	−1.6

[a] Models adjusted for GENDER, AFE (age at first exposure, continuous) and MFE (type of municipality at first exposure).

Table 4. Results of fitting several risk models to the case-cohort data. (OR = odds ratio)

Model	Equation for relative risk (OR for the case-cohort data)[a] as a function of cumulative exposure (x)	Free parameters	Deviance	Exposure (μT-years)	Parameter estimate	Standard error	T-statistic
Multiplicative models[b]							
1	Separate OR each category of cumulative exposure	5	933.4	0.20—0.39	−0.1275	0.2345	−0.54
				0.40—0.99	0.1088	0.2476	0.44
				1.00—1.99	−0.1460	0.4786	−0.31
				≥ 2.00	−0.2574	0.5263	−0.49
2	$OR = \exp(\beta)$	2	932.5	All	−0.1466	0.2163	−0.68
3	$OR = \exp(\beta x + \gamma x^2)$	3	931.0	All	0.1694	0.3205	0.53(β)
					−0.07955	0.09767	−0.81(γ)

[a] Models adjusted for MFE (type of municipality at first exposure) in multiplicative terms.
[b] No maximum likelihood solution was found for the additive relative risk models and the additive models using case-cohort data.

Appendix 4

Additional risk assessments based on the case-cohort data

Table 1. Risk of acute myeloid leukemia by other exposure estimates. (OR = odds ratio, 95% CI = 95% confidence interval)

Exposure criterion	Cases	OR[a]	95% CI
Highest exposure			
Polytomous exposure			
< 0.10 µT	55	1.00	.
0.10—0.19 µT	4	1.12	0.36—3.28
≥ 0.20 µT	1	0.39	0.052—2.96
Dichotomous exposure			
≥ 0.10 µT	5	0.81	0.31—2.12
≥ 0.20 µT	1	0.39	0.052—2.93
≥ 0.30 µT	1	0.58	0.076—4.37
Continuous exposure			
per 1 µT	60	0.74	0.11—5.16
Age at first exposure to magnetic fields of ≥ 0.10 µT			
Polytomous exposure per -1 year	5	0.87	0.67—1.12
Time since last exposure to magnetic fields of ≥ 0.10 µT			
Dichotomous exposure			
≥ 3 years	3	1.60	0.25—10.24
≥ 6 years	2	1.86	0.18—18.74
≥ 9 years	1	4.63	0.39—54.65
Polytomous exposure			
per 1 year	5	1.07	0.84—1.38

[a] Matched odds ratio, adjusted for type of municipality.

Table 2. Risk of chronic myeloid leukemia by other exposure estimates. (OR = odds ratio, 95% CI = 95% confidence interval)

Exposure criterion	Cases	OR[a]	95% CI
Cumulative exposure			
≥ 0.40 µT-years	3	0.55	0.16—1.91
per 1 µT year	30	0.25	0.035—1.75
Highest exposure			
≥ 0.10 µT	1	0.26	0.034—1.93

[a] Matched odds ratio, adjusted to type of municipality.

Table 3. Risk of acute lymphatic leukemia by other exposure estimates. (OR = odds ratio, 95% CI = 95% confidence interval)

Exposure criterion	Cases	OR[a]	95% CI
Highest exposure			
≥ 0.10 µT	4	4.91	1.18—20.36
≥ 0.20 µT	2	3.98	0.64—24.66

[a] Matched odds ratio, adjusted to type of municipality.

Table 4. Risk of other types of leukemia (excluding acute myeloid, acute lymphatic, chronic myeloid and chronic lymphatic leukemia) by other exposure estimates. (OR = odds ratio, 95% CI = 95% confidence interval)

Exposure criterion	Cases	OR[a]	95% CI
Cumulative exposure			
≥ 0.40 µT-years	2	0.70	0.16—3.11
≥ 1.00 µT-years	2	1.65	0.34—7.94
≥ 2.00 µT-years	1	1.47	0.16—13.39
per 1 µT year	21	0.93	0.47—1.85
Highest exposure			
≥ 0.10 µT	2	1.07	0.23—5.02
≥ 0.20 µT	1	1.14	0.13—9.73

[a] Matched odds ratio, adjusted to type of municipality.

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