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***E**lectromagnetic fields and health effects—epidemiologic studies of cancer, diseases of the central nervous system and arrhythmia-related heart disease*

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English summary

Johansen C. Electromagnetic fields and health effects—epidemiologic studies of cancer, diseases of the central nervous system and arrhythmia-related heart disease. *Scand J Work Environ Health* 2004;30 Suppl 1:1–80.

This epidemiologic investigation comprised separate studies of the risk of cancer, cause-specific mortality rates, risks for neurodegenerative diseases, and the risk of arrhythmia-related heart disease among employees exposed to extremely low-frequency (50-Hz) electromagnetic fields (EMF) in the Danish utility industry. All the employees in this industry were followed-up in several registers. The risk of disease was analyzed in relation to occupational exposure to EMF, latency, and duration of employment. A specific job-exposure matrix was developed and validated by comparison with direct measurements of EMF during a workday. Linkage with the Danish Cancer Register did not identify increased risks for the cancers suggested a priori to be associated with exposure to EMF, including leukemia, brain tumors, and breast cancer. Significantly increased risks for lung cancer and mesothelioma were identified for workers highly exposed to asbestos. Linkage with the National Mortality Register revealed a significantly increased overall mortality rate from amyotrophic lateral sclerosis (ALS), with an increasing trend with duration of employment and EMF exposure. In addition, a significantly increased mortality rate from electric accidents was observed. It was hypothesized that the observation of increased mortality from ALS was associated with exposure to EMF or electric shocks. No increased mortality rate from cardiovascular or cerebrovascular disease was observed. Linkage with the National Hospital Register also revealed an increased risk of ALS and, thereby confirmed the finding of an increased mortality rate for this disease in the previous study. Linkage of the cohort with the Multiple Sclerosis Register revealed an increased risk of multiple sclerosis, which was not, however, significant. Linkage with the Pacemaker Register showed no increased risk of severe arrhythmia-related heart disease.

The second part of the study included the establishment of a large, nationwide cohort of mobile phone subscribers comprising some 420 000 persons. No increased risk was observed for the cancers considered a priori to be possibly associated with the radiofrequency fields emitted by mobile phones, which were brain tumors, including acoustic neuroma, salivary gland tumors, and leukemia. The data were analyzed by duration of phone use, latency, system used (NMT, GSM or both) and age at first subscription. A study of the incidence of ocular malignant melanoma in comparison with the annual increase among the mobile phone subscribers showed a highly stable incidence rate for this rare cancer in Denmark over close to 50 years of registration.

On the basis of these studies and the scientific literature, it is concluded that occupational exposure to 50-Hz EMF is not associated with an increased risk of cancer, but that these fields, electric shocks, or some other unknown factor related to alternating current electricity may be associated with the risk of ALS. There is no clear evidence that 50-Hz EMF is associated with other neurodegenerative or cardiovascular diseases. At present, there is little, if any, evidence that the use of mobile phones is associated with cancer in adults, including brain tumors, acoustic neuroma, cancer of the salivary glands, leukemia, or malignant melanoma of the eye.

Dansk resumé

Johansen C. Electromagnetic fields and health effects—epidemiologic studies of cancer, diseases of the central nervous system and arrhythmia-related heart disease. *Scand J Work Environ Health* 2004;30 Suppl 1:1–80.

Denne epidemiologiske afhandling omfattede særskilte undersøgelser af risiko for kræft, den årsagsspecifikke dødelighed, risiko for neurodegenerative sygdomme og hjertesygdomme karakteriseret ved hjerterytme forstyrrelser blandt ansatte ved danske elselskaber. Disse hypoteser blev undersøgt i relation til udsættelse for ekstremt lavfrekvente (50-Hz) elektromagnetiske felter (EMF) på arbejdspladsen, latenstid og varighed af ansættelse. En job-eksponerings matrix blev udviklet og valideret ved sammenligning med en mindre stikprøve af direkte målinger af eksponering for 50-Hz EMF over en hel arbejdsdag. Gennem en kobling af hele kohorten til det danske Cancer Register blev der ikke observeret en signifikant øget risiko for de kræftformer der på forhånd var antaget ville være associeret med eksponering for EMF. Disse kræftformer er leukæmi, hjerne tumorer og brystkræft. Der blev observeret en signifikant øget risiko for lungekræft og lungehindekræft i blandt ansatte som i deres arbejde var højt eksponeret for asbest. I en undersøgelse af den årsagsspecifikke dødelighed blev der observeret en signifikant øget dødelighed af amyotrof lateral sclerose (ALS) blandt ansatte som var stigende med ansættelseslængde og udsættelse for EMF. Samtidig blev der observeret en signifikant øget dødelighed af elektriske ulykker. Det blev diskuteret om denne forøgede risiko for ALS kunne forklares ved eksponering for EMF eller for elektriske ulykker. I denne undersøgelse blev der ikke fundet en øget dødelighed af hjerte- og karsygdomme. En koblingsundersøgelse til Lands Patient Registret bekræftede fundet af en øget forekomst af ALS blandt ansatte ved danske elselskaber. En kobling til det danske Sclerose Register viste en øget nonsignifikant risiko for dissemineret sclerose. En kobling af kohorten til det danske Pacemaker Register viste ingen øget risiko for implantation af pacemakere, som tegn på rytmeforstyrrelser i hjertet.

I den anden del af afhandlingen indgår dannelsen af en kohorte af danske abonnenter til mobiltelefoner. Kohorten inkluderede omkring 420.000 mennesker, der ikke havde en øget risiko for kræft sammenlignet med befolkningen i øvrigt. Særligt var der ikke en øget risiko for hjerne tumorer, herunder akoustikus neurinomer, spytkirtel cancer og leukæmi. Analysen af kræftisiko var stratificeret med hensyn til varighed af abonnement, latenstid, det system den enkelte anvendte (NMT og/eller GSM) og alder ved første abonnementsdato. Den sidste undersøgelse i afhandlingen sammenlignede den årlige tilvækst i antallet af mobiltelefonabonnenter med forekomsten af melanom i øjet. Der blev ikke fundet at forekomsten af den sjældne kræftsygdom i Danmark gennem næsten 50 år afspejlede den eksponentielle vækst i antallet af mobiltelfon abonnenter.

Med udgangspunkt i resultaterne af disse undersøgelser og den videnskabelige litteratur i øvrigt kan det konkluderes, at erhvervsmæssig udsættelse for 50-Hz elektromagnetiske felter ikke synes at øge risiko for kræft, men at disse elektromagnetiske felter, elektriske chok eller en anden ukendt faktor der er knyttet til vekselstrøms elektricitet muligvis øger risiko for ALS. Der er ikke tilstrækkelig evidens for at 50-Hz elektromagnetiske felter øger risiko for andre neurodegenerative sygdomme eller hjerte- og karsygdomme. I øjeblikket er der kun en ringe, hvis overhovedet nogen, evidens for at mobiltelefoner er en risikofaktor for kræft blandt voksne inklusiv hjernesvulster, herunder akoustikus neuromer, maligne spytkirtel tumorer, leukæmi eller melanom i øjet.

This dissertation is based on the following publications, referred to in the thesis by their Roman numerals:

- I. Johansen C, Olsen JH. Risk of cancer among utility workers—a Danish cohort study. *Am J Epidemiol* 1998;147:548–55.
- II. Johansen C, Olsen JH. Mortality from amyotrophic lateral sclerosis, other chronic disorders, and electric shocks among utility workers. *Am J Epidemiol* 1998;148:362–8.
- III. Johansen C, Koch-Henriksen N, Rasmussen S, Olsen JH. Multiple sclerosis (MS) among utility workers. *Neurology* 1999;52:1279–82.
- IV. Johansen C. Exposure to electromagnetic fields and risk of central nervous system disease in utility workers. *Epidemiology* 2000;11:539–43.
- V. Johansen C, Boice JD, McLaughlin JK, Olsen JH. Cellular telephones and cancer—a nationwide cohort study in Denmark. *J Natl Cancer Inst* 2001;93:203–7.
- VI. Johansen C, Raaschou-Nielsen O, Skotte J, Thomsen BL, Olsen JH. Validation of a job-exposure matrix for assessment of exposure to electromagnetic fields of utility workers. *Appl Occup Environ Hyg* 2002;17:304–10.
- VII. Johansen C, Boice JD Jr, McLaughlin JK, Collatz Christensen H, Olsen JH. Mobile phones and malignant melanoma of the eye. *Br J Cancer* 2002;86:348–9.
- VIII. Johansen C, Feychting M, Møller M, Arnsbo P, Ahlbom A, Olsen JH. Risk of pacemaker implantation in male utility workers—a nationwide cohort study. *Am J Epidemiol* 2002;156:857–61.

Abbreviations

ALS	amyotrophic lateral sclerosis
CI	confidence interval
CNS	central nervous system
DNA	deoxyribonucleic acid
ELF	extremely low frequency
EMF	electromagnetic field(s)
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
JEM	job-exposure matrix
MS	multiple sclerosis
RF	radiofrequency
ROS	reactive oxygen species
SIR	standardized incidence ratio

Introduction

Industrialization is characterized by an increasing production, distribution, and consumption of electricity. In Denmark, the use of electricity has increased by more than 30-fold in the past 55 years, from less than 1000 GW hours in 1945 to 32 849 GW hours in 2000 (1). Apart from the risk of fatal accidents due to electric shocks, electricity has been considered to have improved the general quality of life, including general health. In 1979, however, Wertheimer & Leeper observed that children living in homes classified as exposed to electromagnetic fields (EMF) in the extremely low-frequency (ELF) band (eg, 50–60 Hz) were at higher risk of leukemia, lymphoma, and nervous system tumors than unexposed children (2). Numerous published studies subsequently reported increased risks for childhood cancers, in particular leukemia, as summarized by Ahlbom et al (3) and Greenland et al (4). The observation was followed by the convening of several national committees in industrialized countries to review the scientific literature on exposure to EMF and the risk of cancer in order to evaluate the need for further regulations or legislation concerning exposure to EMF (5, 6). Most recently, the International Agency for Research on Cancer (IARC) conducted a thorough evaluation of the carcinogenic risk of EMF to humans. The main conclusion was that ELF magnetic fields are possibly carcinogenic to humans; this conclusion was based on consistent, statistically significant associations with high-level residential exposure to magnetic fields, with a doubling of the risk for childhood leukemia among children exposed to more than 0.4 μ T. In contrast, no consistent evidence was found that childhood exposure to ELF EMF was associated with brain tumors or any other kind of solid tumor (7).

If ELF EMF are carcinogenic, persons occupationally exposed to this agent would be expected to be at increased risk of cancer, including leukemia, brain tumors, and breast cancer. In several studies published during the 1980s, of persons occupationally exposed to EMF, increased risks of leukemia and brain tumors were found, with smaller increases in the risk of lymphoma, breast cancer, and malignant melanoma. These results stimulated numerous studies on the possible association between this exposure and risks for cancer, including the studies summarized in the present thesis.

It was suggested recently that occupational exposure to ELF EMF increases the risk of a number of diseases of the central nervous system (CNS), including amyotrophic lateral sclerosis (ALS), Alzheimer's disease, and

Parkinson's disease, due to exposure to either EMF or electric shocks (8). It was further suggested that occupational exposure to ELF EMF increases the risk of cardiac arrhythmia-related conditions and acute myocardial infarction (9). The latter hypothesis was based on observations in a double-blind laboratory investigation in which exposure to 20 μ T of intermittent 60-Hz magnetic fields was found to reduce the normal variation in the heart rate reversibly (10).

Some experimental studies have indicated that exposure to radiofrequency (RF) fields in combination with exposure to a weak, known carcinogenic agent increases the incidence of tumors and tumor growth. At the same time, the possibility that the thermal effects are carcinogenic per se cannot be ruled out. A few studies on animals suggested that RF fields promote tumor growth; however, these studies have been criticized on methodological grounds (limited size, lack of control for other sources of exposure in the laboratory, anatomic focus of exposure, level of exposure, and length of time for which the animals were exposed) (11). Nevertheless, the overall conclusion from these studies is that cell or tissue processes that are known to be related to carcinogenesis may be influenced by exposure to EMF at frequencies similar to those generated by mobile phone equipment.

The widespread use of mobile telephones and other devices that increase exposure to RF EMF has raised the question of possible health effects, including cancer, mainly due to the thermal nature of RF fields (12), although it has been speculated that nonthermal mechanisms have biological effects (11).

Physics

Electromagnetic fields of frequencies less than 100 kHz

EMF are composed of electric fields and magnetic fields. These fields are produced by a wide range of electric devices, including appliances such as washing machines, electric shavers, and microwave ovens, around wiring and by lightning, in dwellings and near electric power lines. Heavy exposure to EMF can occur only in the vicinity of high-voltage overhead transmission lines, close to transformers and underground cables, and also close to large electrical machinery. Magnetic flux density (B) is measured in teslas (T), and it is related to the electric field (H). The exposure of people who

live close to high-voltage overhead transmission lines in Denmark or who are occupationally exposed to magnetic fields can be between milliteslas (10^{-3}) and microteslas (10^{-6}) (13).

As shown in figure 1, the electromagnetic spectrum covers a wide range of fields, including 50 Hz, used in the power supply in Denmark, RF fields (30 kHz to 300 GHz), used in broadcasting and mobile telephones, X-rays, used in medical diagnosis, and gamma radiation, used in cancer treatment.

Electromagnetic fields of frequencies between 100 kHz and 300 GHz

EMF waves of frequencies between 100 kHz and 300 GHz are included in the RF range of the electromagnetic spectrum. The region close to a source is called the near field. Here, the electric and magnetic fields are not necessarily perpendicular and are not always characterized as waves. RF fields are often nonpropagating in nature and may be called induction fields. Near fields often vary rapidly with distance. At greater distances from the source, RF fields are known as far fields (plane waves). Assessments of exposure in studies of the association between RF fields and the risk of disease have not been based on direct measurements; instead RF-emitting devices have been used as means of approximating the exposure.

Exposure to electromagnetic fields

Unlike ionizing radiation, to which natural sources contribute the greater proportion of the exposure to the population, man-made sources dominate exposure to

time-varying nonionizing EMF. The natural EMF to which people are unavoidably exposed derive from the static fields arising from current flow in the earth's surface, which gives rise to a magnetic field of 30–70 μT over the surface of the planet, depending on location. The most common time-varying ELF EMF to which people in Denmark and other industrialized countries are continually exposed are those arising from 50–60 Hz electrical power transmission and distribution, electrical appliances, and some radio and television transmitters (table 1). In recent years, mobile telephones have become an important source of exposure to RF fields, and the continued marketing of other portable electronic devices will undoubtedly increase the overall exposure to such fields in the future.

In a Danish study of personal exposure to ELF EMF among employees in the utility industry, persons living close to power lines, office workers, industrial workers, and others, it was observed that people living in dwellings with no nearby high-power line had a geometric mean exposure of 0.04 μT , corresponding to half the exposure of office workers. In homes near high-power lines, the average geometric mean exposure was 0.29 μT , the highest value being 2.24 μT . During workhours, employees in the industry were exposed an average of 6 μT , and utility workers were exposed to a geometric mean of 0.37 μT , but with large variations (14). National variations in residential and occupational exposure to EMF can be explained by differences in distribution systems, wiring configuration (how cables are placed in relation to each other in terms of electric charge), national regulations on exposure, and, to a minor extent, differences in the dosimeter characteristics used for exposure assessment (7).

Mobile telephones transmit RF fields from their antennas and from circuit elements inside the handset. The

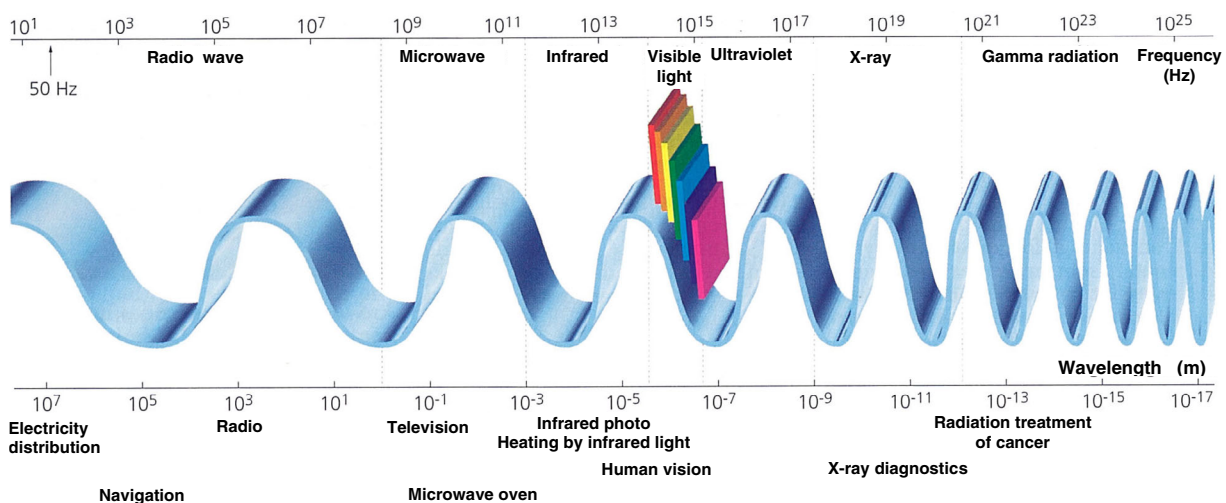


Figure 1. Electromagnetic spectrum, covering a wide range of fields, including 50 Hz, used in the power supply in Denmark, radiofrequency fields (30 kHz to 300 GHz), used in broadcasting and mobile telephones, X-rays, used in medical diagnosis, and gamma radiation, used in cancer treatment.

Table 1. Resultant broadband magnetic field calculated at 5, 50, and 100 cm from appliances for which valid data could be derived on the basis of measured fields at 5, 30, 60 and 100 cm (7).

Type of appliance	Magnetic field (μ T) computed from direct measurements at discrete distances from the surface of appliances						
	N	5 cm	SD	50 cm	SD	100 cm	SD
Television	73	2.69	1.08	0.26	0.11	0.07	0.04
Vacuum cleaner	42	39.53	74.58	0.78	0.74	0.16	0.12
Hair dryer	39	17.44	15.56	0.12	0.10	0.02	0.02
Microwave oven	34	27.25	16.74	1.66	0.63	0.37	0.14
Washing machine	34	7.73	7.03	0.96	0.56	0.27	0.14
Clock radio	32	2.34	1.96	0.05	0.05	0.01	0.01
Fridge or freezer	23	0.21	0.14	0.05	0.03	0.02	0.01
Radio	23	3.00	3.26	0.06	0.04	0.01	0.01
Tumble dryer	7	3.93	5.45	0.34	0.42	0.10	0.10
Food mixer	6	69.91	69.91	0.69	0.69	0.11	0.11
Computer	6	1.82	1.96	0.14	0.07	0.04	0.02
Shaver, electric	1	164.75	.	0.84	.	0.12	.

antenna is usually a few centimeters long, either extending from or hidden inside the mobile telephone. Close to the antenna, in the near-field region, a considerable amount of electromagnetic energy oscillates perpendicularly in the outward direction from and along the antenna. The E and B fields are still at right angles to each other, but they are not in phase, and their values can differ from the expressions that apply to the far field (11). When the antenna of a mobile telephone is near the body, the RF fields penetrate (eg, the skull); however, the fields inside the head are three times smaller than those outside when the antenna is 1.4 cm from the surface of the head. In addition to RF fields, fields of these same frequencies, a few microteslas in magnitude, are generated by currents flowing from the battery of the mobile telephone.

Biological mechanisms

Extremely low-frequency electromagnetic fields and cancer

To date, there is no convincing evidence that EMF in the 50-Hz frequency, encountered in the general environment or during work, interact with biological systems to initiate or promote cancer by one or more mechanisms. The electric currents induced by EMF are several orders of magnitude weaker than currents occurring naturally in the human body. Theoretically, the amount of energy produced by EMF is insufficient to break deoxyribonucleic acid (DNA) molecules or other chemical bonds. Some of the proposed mechanisms by which ELF EMF could cause cancer are a direct genotoxic effect in exposed persons (15–18), changes in the intracellular calcium ion concentration (19–21) and effects on the 6-hydroxy melatonin sulfate concentration (22–25).

While biological effects that may be linked directly or indirectly to the multistep cellular mechanism for carcinogenesis have been reported in individual studies, the scientific literature contains many conflicting observations. Furthermore, some of the positive observations have been based on experimentally limited studies. Many of the systems used to investigate possible mechanisms have failed to provide evidence of an effect, and, when effects have been reported, other laboratories have often been unable to reproduce them.

Extremely low-frequency electromagnetic fields and neurological diseases

Several epidemiologic studies have suggested that exposure to EMF increases the risk of diseases of the CNS, such as Alzheimer's disease, ALS, epilepsy, and Parkinson's disease. Although specific suggestions have been made for each of these diseases, oxidative stress appears to be a common factor. During the reduction of oxygen in mitochondria, three intermediate reactive oxygen species (ROS) are produced. Cells that receive toxic shocks from exposure to EMF may produce larger quantities of ROS than can be contained by the usual cellular antioxidant mechanisms. ROS increase leakage through the cell membrane by acting on polyunsaturated fatty acids; subsequently the influx of calcium and sodium ions increases, and this increase, in turn, may initiate apoptosis (natural cell death) or the production of protein kinase C, which is involved in the formation of tau and amyloid metabolism, which are characteristic components of ALS and Alzheimer's disease, respectively (26–27). In contrast to the effect of EMF, it has been suggested that exposure to electric shocks may increase the risk of ALS. Electric currents may damage brain tissue by disturbing circulation. It has also been speculated that severe electric shocks cause a massive

synchronized discharge of neurons, and this discharge may release sufficient glutamate to precipitate toxic changes, as has already been outlined (27). No consistent mechanism has been identified, however, that could explain the observed association between exposure to EMF or electric shocks and these neurodegenerative diseases.

Extremely low-frequency electromagnetic fields and heart disease

Reductions in specific components of heart rate variation have been shown to predict the risk of heart diseases in several large prospective cohort studies (28–31). A reduction in heart rate variation also appears to predict overall mortality among people who survive myocardial infarction (32), and it further increases the risk of sudden cardiac death (33). The hypothesis that exposure to ELF magnetic fields influences specific subtypes of cardiac disorders arose from a study of acute cardiac effects among volunteers. In a double-blind experiment, exposure to 20 μ T of intermittent 60-Hz magnetic fields reversibly reduced the normal variation in heart rate (10).

Radiofrequency electromagnetic fields and cancer

The biological process underlying a possible association between exposure to mobile telephones and the risk of cancer has been proposed to be a thermal or nonthermal mechanism that promotes tumor growth (34). The term “thermal” implicates a rise in temperature, whereas nonthermal effects are those that occur in experimental

situations in which a temperature rise is avoided. The potential carcinogenicity of RF was broadly debated when Lai & Singh (35, 36) reported increased numbers of DNA breaks in rat brain cells after 2-hour exposures to RF radiation of 2450 MHz. Subsequent studies, however, failed to replicate the findings (37–39). An experimental study, yet unreplicated, has been reported in which an excess of lymphoma was found in transgenic mice predisposed to this tumor. The mice were exposed for 18 months to pulse-modulated RF fields, similar to those used in digital mobile telephones (900 MHz), and were found to have a significantly increased risk of lymphoma (40). Other studies have not found carcinogenic effects, and the evidence for tumor initiation or promotion by these frequency bands is limited (12).

Aim

In this thesis I have investigated the hypothesis of an association between occupational exposure to time-varying ELF EMF and the risks of cancer (*study I*), neurological disease (*studies II, III, and IV*) and severe arrhythmia-related heart diseases (*study VIII*). In *study VI*, the job-exposure matrix (JEM) used in these studies was validated. The association between exposure to RF EMF and the risk of cancer was investigated in two studies (*studies V and VII*).

These studies were approved by the Danish Data Protection Agency (J.nr 1994–1200–301, 1997–2160–253, 2001–41–0520, and 1996–1200–121).

Material and methods

This thesis consists of eight studies, based on (i) a cohort of all employees in all Danish utility companies, the cohort being used to investigate the hypotheses of an association between occupational exposure to ELF EMF and the risk of cancer, cause-specific mortality, the risk of multiple sclerosis, the risk of neurodegenerative diseases

of the CNS, the risk of pacemaker implantation, and validation of the JEM used in these studies; (ii) a study of all users of mobile telephones in Denmark and the risk of cancer; and (iii) an ecological study contrasting the incidence rates of ocular malignant melanoma in Denmark with the number of mobile telephone subscribers.

Occupational exposure to extremely low-frequency electromagnetic fields

Cohort definition

The basic cohort consisted of all employees at all 99 utility companies that supply electricity in Denmark. The companies were established between 1900 and 1979 as either private enterprises or publicly owned companies. Some produced, transmitted, and distributed electricity, whereas others provided only one or two of these services. The cohort members were recruited with a questionnaire sent to all the electricity companies, informing the administrative staff about the study and asking each company to provide information on all persons employed since the establishment of the company. For each employee, the information included name, date of birth or personal identification number, date of employment(s), date(s) of leaving, job title, and worktasks at the company. The companies provided information on 38 067 persons employed between 1908 and 1993. In order to evaluate the information obtained from the companies and to avoid selection bias, two searches were conducted in public administrative registers. First, information was retrieved on all employees in the privately owned companies by giving the Danish Supplementary Pension Fund the tax number of each utility company. This pension scheme was established in 1964 and is compulsory for wage earners 18–66 years of age. It retains personal data on the employee, the period(s) of employment at each company, and a branch coding. The personal identification number in combination with the tax number of each company reveals information about the employment histories of each person, but no information on job title or worktask (41). Subsequently, a list of all persons identified from the tax numbers in the Danish Supplementary Pension Fund was completed by the administrative staff at each privately owned utility company, who added information on job titles and worktasks for the employees not previously identified, partly from memory. Through this procedure, an additional 8217 employees were added to the cohort. Second, a list of all employees in the publicly owned companies was compared with information from the public payroll administration (KommuneData) for the years 1988–1993. No missing employees were identified. The total cohort therefore consisted of 46 284 employees in all 99 utility companies who had first been employed between 1908 and 1993.

Vital statistics

Record linkage with the Central Population Register provided vital statistics. Since 1 April 1968 this register has assigned a unique 10-digit number to all

residents of Denmark; the number includes date of birth and sex. The information in this register is updated continuously. With this linkage procedure, 45 705 employees (98.7%) who were alive on 1 April 1968 were identified. Additional information on date of death, date of emigration, or date of disappearance was provided. No follow-up was possible for employees who had died before 1 April 1968 (N=464), and an additional 115 employees were not traced, primarily because of errors in date of birth, names, or date of emigration. It was decided to exclude these cohort members, and an additional 177 employees for whom the date of first employment was missing. Finally, we restricted the cohort to the 32 006 persons who had been employed for at least three consecutive months in one of the 99 utility companies (table 2).

Exposure assessment

Four engineers experienced in the planning and operation of utility companies were asked to establish a JEM

Table 2. Descriptive characteristics of 31 990 workers with at least 3 months' employment at a Danish utility company. (EMF = electromagnetic field)

Characteristic	Men (%) (N=26 124)	Women (%) (N=5866)	Either sex (%) (N=31 990)
Employees			
Blue-collar workers	85	46	79
White-collar workers	15	54	21
Year at first employment			
1900–1919	<1	<1	<1
1920–1939	2	<1	2
1940–1959	14	7	12
1960–1979	54	50	54
1980–1993	30	43	32
Age at first employment			
10–19 years	9	28	12
20–29 years	43	37	42
30–39 years	24	17	22
40–49 years	14	11	13
50–59 years	8	5	8
≥60 years	2	1	2
Length of employment			
<1 years	21	28	22
1–4 years	29	37	30
5–9 years	17	16	17
10–19 years	15	11	14
≥20 years	19	8	17
Exposure to 50-Hz EMF			
Background (<0.09 µT)	17	21	18
Low (0.1–0.29 µT)	11	61	20
Medium (0.3–0.99 µT)	29	14	26
High (>1.0 µT)	27	2	23
Unknown	16	2	13
Exposure ^a to asbestos			
Background	66	96	71
Above average	34	4	29

^a Work-related average exposure.

Table 3. Examples of combinations of job title and work area for employees Danish utility companies ranked according to category of average exposure to 50-Hz magnetic fields at work, 1968–1993. (EMF = electromagnetic field)

50-Hz EMF exposure category	Job title
High exposure category ($\geq 1.0 \mu\text{T}$)	
Station (distribution)	Worker, maintenance worker, electrician
Overhead cable department (production and transmission)	Cable splicer, engine mechanics, engineer
Station (production and transmission)	Technical assistant, linemen, general mechanics (master)
Medium exposure category ($0.3\text{--}0.99 \mu\text{T}$)	
Cables and overhead lines (distribution)	Worker, cable splicer (master), linemen (master)
Maintenance guard (production and transmission)	Generator facility worker, maintenance (foremen), engineer (maintenance)
Cleaning (production and transmission)	Worker, skilled worker, maintenance worker
Low exposure category ($0.1\text{--}0.29 \mu\text{T}$)	
Workshop (distribution)	Engine mechanics, electromechanics, technical servicemen
Overhead cables (production and transmission)	Engineer, cable splicer (foremen), cable splicer (linemen)
Administration (production and transmission)	Technical assistant, meter reader, engineer maintenance
Background exposure category ($<0.09 \mu\text{T}$)	
Store (distribution)	Skilled worker, administrative employee, technical servicemen
Administration (distribution)	Cleaning service worker, administration (manager), engineer (manager)
Store (production and transmission)	Skilled worker, administrative employee, technical servicemen

that included job titles and worktasks in production, transmission, and distribution in Danish utility companies. This dedicated JEM was comprised of 25 jobs and 19 worktasks in this industry. Subsequently, the engineers assigned five average levels to exposure to 50-Hz ELF EMF during a workday. The five categories of exposure included background exposure ($<0.09 \mu\text{T}$), low exposure ($0.1\text{--}0.29 \mu\text{T}$), medium exposure ($0.3\text{--}0.99 \mu\text{T}$), high exposure ($>1.0 \mu\text{T}$), and unknown exposure. The scale was based partly on a series of 196 measurements of exposure to 50-Hz EMF for 24 hours for 129 employees in six Danish utility companies. These measurements were conducted in 1993 with personal dosimeters and the sampling of electric and magnetic fields every 5 seconds (14). At the time of the construction of the JEM, access was available to the data only as they appeared in the paper of Skotte (14). Individual assignments were based on the first job held and the related worktask. The administrative staff was specifically asked to include any changes in job titles or worktasks for each employee. According to the company files, only 323 men and 97 women changed their job title or worktask during their employment. It was therefore assumed that the category-specific levels of exposure were unchanged throughout the study period. The estimated cumulative exposure was calculated by multiplying the

average exposure levels by the duration of employment. Table 3 gives examples of combinations of job titles and work areas. The same four engineers established a simple JEM for asbestos in two exposure categories, no exposure and above-average exposure to asbestos at work. Exposure to asbestos or similar materials was not measured directly.

Validation of the job-exposure matrix. In *study VI*, the JEM used as the instrument for exposure assessment in *studies I, II, III, IV* and *VIII* was validated. Altogether 129 workers from six companies were selected to participate in the dosimeter study (14). They were not chosen according to a formal randomization scheme, but were instead selected in collaboration with the companies to cover a broad range of job types and tasks. They were selected from the following five main work environments: generation facilities, transmission lines (voltage $>50 \text{ kV}$), distribution lines (voltage $<50 \text{ kV}$), substations, and other jobs related and unrelated to electricity. The 129 subjects accounted for 2.5% of the workers in the five types of work environment in the utility companies. The measurements were compared with the JEM established for the utility cohort.

Analyses. First, the measured exposure in the four JEM categories was compared with the arithmetic mean, the median, and the geometric mean of the measured values within each JEM exposure category. The 95% confidence interval (95% CI) was calculated to indicate the uncertainty of the geometric mean. In addition a 95% prediction interval was calculated to indicate the likely range within which the true exposure of a person in a given JEM category would be expected to occur. Second, the degree of misclassification among the four categories of JEM-estimated exposure was estimated by dividing the measures into four categories, similar to those used in the JEM, and comparing them with the categories assigned by the JEM. Finally, the probability was calculated that a randomly selected person in one JEM exposure category had greater exposure than a randomly selected person in a lower JEM exposure category. All possible pairs of persons were established for all combinations of JEM exposure categories. For a given combination of two JEM exposure categories, the proportion of pairs with the greatest exposure of the person in the higher of the two JEM categories was calculated on the basis of simple counts.

The validation showed that the JEM used can introduce nondifferential misclassification mainly between adjacent categories of exposure, but that the two extreme categories satisfactorily separated low and very highly exposed workers. If the sample size in the two extreme groups provides enough power, a study in which this JEM is used should allow detection of true associations

between exposure to magnetic fields within these categories and disease. Furthermore, this study found no justification for distinguishing between the two intermediate categories of exposure. The JEM used in *study VIII* was revised in accordance with this finding.

The results of the validation study were reassuring; however, the fundamental problem was a lack of knowledge about which exposure parameters were relevant to the study of the potential health effects of time-varying EMF. There is no accepted, well-defined measure of the biological effects of EMF, and it is not known if they have a monotonous dose-response relationship with the outcome in question. Several aspects of EMF, including the intensity, degree of transience, gradient across the field, frequency, location and duration of exposure may play a role, and it is not possible to say which role. Overall, however, the selected exposure categories separated highly exposed employees from those with little exposure.

Follow-up

Follow-up for cancer. This cohort (N=32 006) was followed for cancer (*study I*) at the Danish Cancer Registry, which has been in operation since 1942 (42). The period of follow-up for cancer occurrence among employees in both privately and publicly owned companies was taken from 1 April 1968 or the date of first employment, whichever came last, to the date of death, emigration, or 31 December 1993, whichever came first. Cancers were classified according to the modified Danish version of the International Classification of Diseases (ICD), seventh revision (ICD-7).

Follow-up for cause-specific mortality. In the study of cause-specific mortality (*study II*), data on the 21 236 men in the cohort were linked to the National Death Certificate files, in which information on mortality has accumulated for more than a century (43). As detailed mortality rates have been available in a computerized format since 1974, the period of follow-up of the cohort members was from 1 January 1974 or the date of first employment, whichever came last, to the date of death, emigration, or 31 December 1993, whichever came first. Causes of death were classified according to the ICD, eighth revision (ICD-8).

Follow-up for multiple sclerosis. In the study of the risk of multiple sclerosis (MS) (*study III*), data on the entire cohort (N=31 990) were linked to the files of the Danish Multiple Sclerosis Registry, which was founded in January 1948 as a nationwide body to register all cases of MS in Denmark. All cases of suspected or verified MS are currently notified to the Registry from all 22 Danish neurological departments and the two rehabilitation centers of the Danish Multiple Sclerosis Society

(44). Only verified cases of MS were included in the present study. The period of follow-up for the occurrence of MS among employees in both privately and publicly owned companies was taken from 1 April 1968 or the date of first employment, whichever came last, to the date of death, emigration, or 31 December 1993, whichever came first.

Follow-up for neurodegenerative diseases. In the study of morbidity from neurodegenerative diseases and other disorders of the CNS (*study IV*), data on the entire cohort (N=30 631) were linked to the population-based National Register of Patients, which records more than 99% of all hospital discharges for somatic diseases (45). Data on all 30 631 employees were linked to the Register for follow-up for CNS diseases between 1 January 1978 or the date of first employment, whichever came last, and the date of death, emigration, or 31 December 1993, whichever came first. For employees who were hospitalized more than once with diseases in the same diagnostic entity (ICD-8), only the first record was included in the analysis; both diseases were counted when the same subject was hospitalized for more than one CNS disease. This disease category was defined as senile dementia (ICD-8, 290.09) and presenility, including Alzheimer's disease (ICD-8, 290.10–290.18), other demyelinating CNS neuropathies (ICD-8, 341), Parkinson's disease (ICD-8, 342.99), cerebral palsy (ICD-8, 344.99), epilepsy (ICD-8, 345), motor neuron disease, including ALS (ICD-8 348.09), progressive bulbar palsy (ICD-8, 348.19) and progressive muscular atrophy (ICD-8, 348.29), and diseases of the spinal medulla (ICD-8, 349). Medical records were obtained for cases of ALS and other motor neuron diseases to verify the diagnosis and to obtain information on episodes of electric shocks or other occupational exposure before development of the disease.

Follow-up for arrhythmia-related heart disease. In *study VIII*, data on the 24 056 men in the cohort were linked to the population-based Danish Pacemaker Register (46) for follow-up for pacemaker implantation from 1 January 1982 or the date of first employment, whichever came last, to the date of death, emigration, or 31 December 2000, whichever came first. Each Pacemaker Register record contains the date of pacemaker implantation, the name of the hospital and cardiological department in which the implantation was performed, and the type of pacemaker and lead implanted.

Analyses

In *studies I, II, III, IV, and VIII*, national incidence rates, by gender and 5-year age groups and calendar-year periods for the outcome of interest, were applied to the

person-years under observation for the entire cohort in order to obtain the number of cases expected had the cohort members experienced the same rate of the outcome as that observed in the general population. Tests of significance and 95% confidence intervals for the standardized incidence ratio (SIR), taken as the ratio of observed to expected numbers of cancers, were calculated using the Miettinen exact confidence interval when the observed number of cases was small; otherwise, an accurate asymptotic approximation was used. The relation between specific exposures to ELF EMF and cumulative exposures and time since first employment (latency) and the risk of the outcome was analyzed. In *study I*, information on exposure to asbestos was included in a stratified analysis of risk of lung and pleural cancer.

In *studies IV and VIII*, the data were also analyzed with a multiplicative Poisson regression model that included age, duration of employment, calendar year, and level of exposure to ELF EMF as defined by the JEM. The Poisson regression model allows internal comparison between groups of employees with different exposures to ELF EMF.

Exposure to radiofrequency electromagnetic fields and risk of cancer

Study V

Cohort definition. *Study V* was based on a cohort of mobile phone subscribers, identified from a roster of all subscribers in Denmark between 1 January 1982 and 31 December 1995. The subscribers were identified from the computerized files of the two Danish operating companies, Sonofon and TeleDanmarkMobil, which included the name of the subscriber (either a person or a company), the address according to parish, postal code, street, building number, floor and side of the building, the type of telephone system used (analogue telephones were either NMT 450 or NMT 900, and digital telephones were GSM), and the date of subscription(s). For users of the digital system, the date of termination of subscription(s) or last invoice mailed was also provided, and the information enabled the computation of the duration of subscription in months. A total of 723 421 subscribers were initially identified; 200 507 corporate customers were excluded because information on individuals was not available.

Vital statistics. The names and addresses of the remaining 522 914 subscribers were linked to the files of the Central Population Register to verify the personal data and obtain individual personal identification numbers and information on vital status, date of death, or date of emigration, if applicable. Linkage to the Central Population

Register further reduced the size of the cohort because of errors in either the name (N=49 352) or the address (N=10 183) of the telephone user or because the address was not residential (N=11 687). The linkage unambiguously identified 451 679 subscribers (86.4%) by name, address, identification number, and vital status. Additional exclusions included 10 679 duplicates, 17 921 whose initial subscription was after 1995 when the recruitment period ended, 2550 persons under the age of 18 years at first subscription, 394 persons permanently residing in Greenland or the Faroe Islands, and 53 persons who requested not to be included in the cohort after learning about the study through media announcements. The final cohort consisted of 420 095 mobile telephone subscribers or 80.3% of the residential subscribers obtained from the phone company lists.

Exposure assessment. The information on each subscriber included date of first subscription and, for users of the digital system, also date of termination or last invoice mailed, which enabled calculations of duration of subscription. Furthermore, information on age at first subscription was obtained through these linkage procedures.

Follow-up for cancer. Follow-up for cancer was conducted in the Danish Cancer Registry, from the date of first subscription to the date of death, emigration, or 31 December 1996, whichever came first. Cancers were classified according to the modified Danish version of ICD-7 and the risk of intracranial tumors was evaluated by morphology and topography groupings (ICD-O).

Analyses. Danish incidence rates for each cancer, calculated according to gender, 5-year age groups and 5-year calendar periods, were applied to the person-years of observation in the study cohort to obtain the number of cancers expected. Tests of statistical significance and confidence intervals for the standardized incidence ratios were calculated by the Miettinen exact method when the observed number of cancers was small (N<5); otherwise, an accurate asymptotic approximation was used. The relationships between duration of subscription (defined as the aggregated periods of mobile telephone subscriptions) and time since first subscription (latency) and the risk of cancer were evaluated. The analysis was conducted for all subscribers combined and for subcohorts defined by type of mobile telephone system used (analogue only, digital only and persons who used an analogue and later a digital phone).

Study VII

Sample definition. *Study VII* included all cases of ocular malignant melanoma identified between 1943 and 1996 by the Danish Cancer Registry and classified according

to the modified Danish version of ICD-7. Data on subscribers to mobile telephones in Denmark in 1982–1996 were obtained from the National Board of Telecommunication.

Analyses. The age-specific incidence rates were calculated in 5-year age intervals and 5-year period intervals. Incidence rates were age-standardized to the world standard population.

Results

Occupational exposure to extremely low-frequency electromagnetic fields

Cancer

A small but significantly increased risk of cancer was observed (SIR 1.06, 95% CI 1.03–1.10). The slight increase was due mainly to statistically significant excesses of cancers of the pleural cavity (SIR 3.2, N=36) and gall bladder (SIR 1.5, N=24) and nonmelanoma skin cancer (SIR 1.2, N=396) among men and cancer of the lung among men (SIR 1.1, N=523) and women (SIR 1.5, N=34) (table 4).

The risks were not increased for leukemia and brain cancer among men; in fact, a reduction of borderline statistical significance was found in the number of brain cancers among men, and no excess was seen for any of the major subtypes of leukemia included in the analysis. Only two cases of breast cancer were found in men, with four expected; the risk of breast cancer among female employees was slightly but nonsignificantly elevated (SIR 1.1, N=96). No trend in risk could be distinguished for leukemia or cancers of the brain or breast in any group of workers, and there was no indication of a link between cumulative exposure to EMF and the risk of any of these tumor types. No pattern of associations that would suggest a link was revealed in additional analyses of duration combining background and low exposures to EMF in one category and medium and high exposures in another. The occurrence of cancers of the lung and pleural cavity also seemed to be unrelated to the level of exposure to EMF. The excesses of these cancers were confined mainly to workers in jobs involving exposure to asbestos.

Several epidemiologic studies have been conducted to investigate the possible association between occupational exposure to ELF EMF and the risk of cancer. The

initial studies linked occupational data from national censuses with information on cancers from nationwide and population-based cancer registries or mortality statistics. Later studies were based on information on employment in jobs assumed to be associated with high exposure to EMF, and in more recent studies EMF were measured at the workplace or measurement protocols were used for samples of study participants. Additional methodological improvements were the inclusion of information on exposure to possible confounders in the workplace and JEM development. Some studies combined occupational and residential exposures.

The initial studies published in the 1980s and early 1990s pointed to an increased risk, but later studies overall did not confirm the early reports. Although there were reports of increased risks for leukemia among persons exposed occupationally to medium or high levels (47–51) for brain tumors (47, 51, 52) and for breast cancer among women (53–56), refinements of epidemiologic methods led to a reduction in the number of studies reporting a positive association between exposure to ELF EMF and the risk of cancer. In line with this trend, the results of the Danish study of utility employees (*study I*) did not support an association between exposure to ELF EMF and the risk of cancer. The conclusion reached by the expert group convened by IARC in relation to leukemia and brain cancer was that there was no consistent exposure-response relationship across studies and no consistent association with specific subtypes of leukemia or brain tumors. Evidence for cancer at other sites was not adequate for evaluation (7).

The results of the experimental research leaves doubt that any real biological link exists between exposure to ELF EMF and cancer. Epidemiologic studies may have gone as far as they can in addressing the potential role of ELF EMF in cancer causation.

Table 4. Observed incident cancers of the breast and the central nervous system (CNS) and leukemia among 26 135 men and 5871 women employed in Danish utility companies for more than 3 months, by combination of average work-related exposure to electromagnetic fields and duration of employment (cumulative exposure), 1968–1993.^{a, b} (SIR = standard incidence ratio)

Cancer site and duration of employment	Background exposure (<0.09µT)		Low exposure (0.1–0.29µT)		Medium exposure (0.3–0.99µT)		High exposure (>1.0µT)		Unknown exposure	
	Observed (N)	SIR	Observed (N)	SIR	Observed (N)	SIR	Observed (N)	SIR	Observed (N)	SIR
Men										
CNS, total	4	0.5	17	0.9	13	0.7	8	0.7	15	1.2
0–4 years	2	0.7	6	0.7	4	0.6	2	0.4	14	1.4
5–9 years	1	0.5	5	1.5	3	0.9	2	1.2	1	0.3
≥10 years	1	0.3	6	0.8	6	0.6	4	0.9	–	–
Leukemia, total	8	1.0	16	1.0	16	0.9	12	1.1	8	0.6
0–4 years	4	1.3	5	0.9	4	0.8	6	1.4	7	0.7
5–9 years	1	0.6	1	0.4	2	0.8	..	..	1	0.4
≥10 years	3	0.8	10	1.2	10	1.0	6	1.1	..	..
Women										
CNS, total	8	1.1	3	3.3	..	..	..	..	4	1.4
0–4 years	4	1.1	1	1.9	..	..	..	..	4	1.6
5–9 years	..	..	..	..	..	..	..	..	..	..
≥10 years	4	1.9	2	9.2 ^c	..	..	..	..	..	..
Breast, total	63	1.3	2	0.3	..	..	1	1.0	30	1.3
0–4 years	35	1.3	1	0.3	..	..	1	1.5	28	1.4
5–9 years	8	0.7	–	–	..	..	..	..	2	0.7
≥10 years	20	1.1	1	0.6	..	..	..	..	..	..

^a Number of persons: 5670 for background exposure, 6512 for low exposure, 8294 for medium exposure, 7289 for high exposure, and 4241 for unknown exposure.

^b Number of person-years: 106 390 for background exposure, 123 951 for low exposure, 121 878 for medium exposure, 67 458 for high exposure, and 96 710 for unknown exposure.

^c P<0.05

Cause-specific mortality, neurodegenerative disease and arrhythmia-related heart disease

An overall increase was observed for mortality with increasing exposure to EMF, which was due to an increased risk of death from lung cancer. Furthermore, increased risks were observed for death from pleural cancer, bronchitis, and emphysema and a nonsignificantly increased risk of suicide.

A significantly increased risk (mortality and morbidity) was observed for ALS in *studies II* and *IV*. No increased risk of Parkinson's disease or Alzheimer's disease was observed in these two studies, and, in *study III*, no significantly increased risk of MS was observed. In *study IV*, a significantly increased risk of epilepsy was observed in an internal comparison across 50-Hz ELF EMF exposure categories but not in a comparison of the risk of epilepsy in the cohort with that in the general population.

In *study II*, a significantly increased rate of death from ALS was observed, with an increasing trend with length of follow-up since first employment in an electric utility company and the extent of exposure to 50-Hz EMF (table 5). In all 14 cases of death from ALS, ALS was stated as the primary cause of death on the death certificate. The results of *study II* also showed greatly increased mortality rates from accidents caused by electricity (electric shocks), particularly among

employees with medium and high exposure to EMF. The mortality rates from other neurological diseases were not increased, although in previous reports above-average exposure to EMF has been linked to Parkinson's disease and Alzheimer's disease.

This result was confirmed in *study IV*. Male workers in the cohort had an increased risk of all motor neuron diseases combined (SIR 1.89, 95% CI 1.16–2.93), on the basis of 20 cases, confined to the 15 men with a diagnosis of ALS (SIR 1.72, 95% CI 0.96–2.83). Men were also at a nonsignificantly increased risk of other motor neuron disease (SIR 2.75, 95% CI 0.88–6.41), demyelinating disease (SIR 1.90, 95% CI 0.51–4.86, N=4), and senile dementia (SIR 1.16, 95% CI 0.96–1.39, N=122). The risks for other CNS diseases, including presenility and Parkinson's disease, were close to those expected. In the Poisson regression analyses, utility workers were at increased risk of senile dementia, epilepsy, and all motor neuron disease when they were compared according to their occupational exposure to EMF (table 6). The risks for all three diseases increased with increasing level of exposure to EMF.

In *study III*, 32 cases of MS were diagnosed, as compared with 23.7 expected from national incidence rates, to yield an SIR of 1.35 (95% CI 0.92–1.91) (table 7), indicating no significantly increased risk associated with exposure to ELF EMF.

In two studies (*II* and *IV*), one providing the first published data on incident morbidity from neurodegenerative diseases (*study IV*), a significantly increased risk of ALS was observed. The mechanism of this association has not yet been determined. Electric shocks from an alternating 50/60-Hz source in the electrical supply system may cause acute symptoms such as burns and local muscular convulsions or even generalized convulsions similar to an epileptic seizure, depending on the

exposure circumstances. The brains of persons who have died after an electricity-related injury are often characterized by acute edema and small perivascular hemorrhages, predominantly in the medulla oblongata (57). Electricity-related injuries classically involve deep anatomic structures, and the damage to these deep tissues in the extremities may be more severe than visible skin burns, including necrosis of muscles, vessels, nerves, and subcutaneous tissue. The factors that determine the

Table 5. Observed numbers of deaths and standard mortality rates (SMR) for selected causes by estimated average workplace exposure to 50 Hz magnetic fields among 21 236 men employed in Danish utility companies for more than 3 months.

Cause of death	Background exposure (<0.09 µT)		Low exposure (0.1–0.25 µT)		Medium exposure (0.3–0.99 µT)		High exposure (>1.0 µT)	
	Observed (N)	SMR	Observed (N)	SMR	Observed (N)	SMR	Observed (N)	SMR
All causes	474	0.79	1063	0.93	1134	0.96	869	1.12 ^a
All malignant neoplasms	151	0.9	301	1.0	366	1.2 ^a	252	1.2 ^a
Neurological disorders								
Amyotrophic lateral sclerosis (ALS)	1	0.9	4	1.9	5	2.3	4	2.8
Parkinson's disease	1	0.7	3	1.3	0.4	1	0.6	
Multiple sclerosis	—	.	—	.	2	0.9	1	0.8
Senile dementia	—	.	1	0.4	2	0.8	1	0.6
Presenile dementia	—	.	1	1.4	1	.	..	..
Behavioral causes								
Accidents caused by electricity	—	.	2	10.1 ^a	5	26.9 ^a	3	30.8 ^a
Alcoholism	1	0.4	10	1.5	6	0.9	4	1.1
Motor vehicle accidents	4	0.5	24	1.3	12	0.7	9	0.9
Suicide	19	1.0	37	0.8	41	0.9	36	1.4
Cardiovascular diseases								
Acute myocardial infarction	96	0.8	225	1.0	232	1.0	160	1.0
Cardiac arteriosclerosis	38	0.7	98	1.0	79	0.8	85	1.2
Other heart diseases	27	0.9	35	0.7	52	1.0	38	1.1
Cerebrovascular diseases	24	0.6	68	0.9	61	0.8	54	1.0
Respiratory diseases								
Bronchitis and emphysema	20	0.8	50	1.1	48	1.0	41	1.2
Asthma	2	1.1	1	0.3	1	0.3	—	.
Other specified causes	82	0.7	189	0.8	203	0.9	170	1.1
Unknown cause	8	0.9	14	0.8	17	0.9	10	0.9

^a P<0.05.

Table 6. Relative risk (RR) of neurological diseases among 24 850 men employed in Danish utility companies by average estimated level of electromagnetic field (EMF) exposure adjusted for age, calendar period, and duration of employment. (95% CI = 95% confidence interval)

Disease ^a	N	Background exposure (<0.09 µT)	Low exposure (0.1–0.29 µT)		Medium exposure (0.3–0.99 µT)		High exposure (≥1.0 µT)		Unknown exposure	
		RR ^b	RR ^b	95% CI	RR ^b	95% CI	RR ^b	95% CI	RR ^b	95% CI
Senile dementia (290.09)	122	1.00	1.00	0.51–1.95	1.15	0.60–2.19	1.43	0.74–2.77	1.51	0.78–2.94
Presenility (290.10–290.19)	30	1.00	0.68	0.20–2.34	0.72	0.21–2.48	0.92	0.25–3.42	1.21	0.34–4.32
Parkinson disease (342.99)	64	1.00	0.89	0.42–1.87	0.68	0.31–1.49	0.64	0.26–1.54	0.72	0.29–1.79
Cerebral palsy (344.99)	45	1.00	0.50	0.16–1.54	0.88	0.33–2.39	0.78	0.25–2.42	2.57	0.92–7.19
Epilepsy (345)	148	1.00	1.51	0.78–2.95	1.50	0.77–2.94	2.03	1.02–4.05	1.61	0.79–3.29
Motorneuron disease (348)	20	1.00	0.86	0.16–4.71	1.27	0.26–6.32	1.56	0.29–8.53	1.90	0.33–11.13
Spinal medullary disease (349)	13	1.00	1.35	0.14–13.04	1.35	0.14–12.97	0.81	0.05–12.96	3.96	0.43–36.59

^a Code of the 8th revision of the International Classification of Diseases in parentheses.

^b From Poisson regression models with the variables occupational EMF exposure, age, duration of employment, and calendar period as covariates.

Table 7. Observed and expected numbers of cases of multiple sclerosis among 26 124 men and 5866 women employed for more than 3 months in Danish utility companies, 1968–1993. (SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Gender	Observed (N)	Expected (N)	SIR	95% CI
Men	21	17.3	1.2	0.8–1.9
Women	11	6.4	1.7	0.9–3.1
Both genders	32	23.7	1.4	0.9–1.9
0–9 years' latency	18	12.6	1.4	0.8–2.3
10–19 years' latency	10	8.1	1.2	0.6–2.3
>20 years' latency	4	2.9	1.4	0.4–3.5

extent of these effects are current, voltage, tissue resistance, current pathway, and duration of contact (58).

Permanent brain damage to the brain is infrequent among survivors. Depending on the characteristics of the accident, the damage may include neurological symptoms. Early in the past century, neurologists found a clinical appearance compatible with ALS among persons who had had electric shocks (59, 60). Other clinicians suggested that the symptoms were similar to those of MS, Parkinsonian syndrome, or spinal atrophic paralysis (61, 62). It is unlikely that such severe symptoms would be due to direct passage of the current through the brain. Case reports of cerebral symptoms in patients in whom the current passed from the hand through the leg to the ground indicate that the neurological sequelae, including degeneration of ganglion cells, were usually not due to direct contact between the current and neurological tissue but were transmitted indirectly to the brain by circulatory disturbances caused by the electricity (57). The neurological disturbances are probably due to vascular disease that follows the primary damage to the vascular walls and the accompanying vasomotoric nerve fibers (58, 63).

The first epidemiologic study linking ALS with accidental electric shocks was published in 1964. Haynal compared the reported frequency of any previous electric injury among 73 ALS patients and 150 patients with other neurological disorders; 12 of the patients with ALS had been exposed (16%) compared with 5 (3%) in the control group. None of the electric accidents studied had caused unconsciousness or other immediate symptoms. It was speculated that the trauma might have acted as a promoter for latent ALS disease (64). Later studies confirmed an association between electric shocks or electricity-related occupations and ALS (65–71).

More recent studies focused on the association with cancer but also provided information about the association between occupational exposure to EMF and the occurrence of ALS (72–74, *study I*). The observation of accelerated demyelination and neuronal death in brain tissue of experimental animals exposed to electric shocks (75, 76), in combination with the early clinical reports and

early epidemiologic findings (64–69), indicate that the excess of neurodegenerative disease found in people with occupations with exposure to EMF may have been due to repeated electric shocks in specific work functions rather than to exposure to high levels of EMF.

Parkinson's disease (77) and Alzheimer's disease have been associated with exposure to ELF EMF (26, 71–73, 78, 79); however, no increased risk was observed in the Danish studies (*studies II and IV*). In addition, no significantly increased risk of MS was identified in *study III*. The diagnostic criteria for ALS, Parkinson's disease, Alzheimer's disease, and MS are distinct and specific to each disease. Furthermore, the clinical symptoms of each disease distinguish them from other CNS disorders. The observed risk estimates for Parkinson's disease, Alzheimer's disease, and MS, all of which were close to unity, were probably not due to nondifferential misclassification. The studies conducted so far provide no reason to believe that Parkinson's disease is associated with exposure to ELF EMF and only weak evidence to suggest that this exposure could cause Alzheimer's disease.

The finding of an almost twofold significantly increased risk of epilepsy among highly exposed men in *study IV* may be due to chance. To address the hypothesis of an association between electric shocks and neurological diseases further, data were analyzed for a nationwide cohort of men and women who had survived an electric accident involving exposure to a 50/60-Hz electric source (unpublished manuscript: Johansen C, Olsen JH. Risk for neurological diseases among survivors of electric shocks: a nationwide cohort study). We reviewed all the medical records of patients in whom epilepsy was diagnosed after the electricity-related accident. Among the medical records of persons with epilepsy (N=19), three prevalent cases of epilepsy were identified, along with three persons who had had severe skull fractures years before the electricity-related injury, indicating that misclassification and confounding might explain the association observed. Overall, the review of the medical records weakens the possible association between electricity-related injuries and the risk of epilepsy. Furthermore, 11 of the persons with epilepsy were not employed in jobs characterized by above-average exposure to EMF. In addition, only one case of neurological disease was identified among people exposed to high voltages, and the person was assumed to have been exposed to higher levels of EMF than the other patients. Thus the results do not support the hypothesis that EMF cause epilepsy. Contrary to the observations in *study IV*, Håkansson et al (71) observed a decreased mortality rate from epilepsy among highly exposed men (>0.53 μ T) when compared with those with lower exposure (<0.164 μ T) in a Cox-regression analysis. In that study, it was speculated that people with epilepsy probably do not work with equipment run by

strong electrical currents. The authors observed that the death certificates of some of the persons who died of epilepsy notified alcohol abuse. Stratified analysis for the latter cause of death revealed that the negative association between ELF EMF and epilepsy was not due solely to the selection of people without alcohol abuse into highly exposed occupations (71).

Overall, there was no significantly increased risk of a pacemaker implant among employees in the utility companies, based on 135 incident cases of implantation, with 140 expected, yielding a risk estimate of 0.96 (95% CI 0.81–1.14). No clear dose-response pattern emerged with increasing exposure to EMF or duration of employment. The Poisson regression analysis showed a risk of unity (95% CI 0.6–1.5) for the highly exposed group compared with background exposure, and no trend in risk in a comparison with workers according to their occupational exposure to EMF (table 8).

The study of cause-specific mortality in this cohort (*study II*) did not identify increased risks for other cardiovascular diseases, including acute myocardial infarction, cardiac arteriosclerosis, and cerebrovascular disease (table 5). Likewise, Sahl (80), in a cohort of utility workers in southern California in the United States reported no increase in mortality rate in a cohort of 35 391 male workers, including 369 cases of chronic coronary heart disease and 407 cases of myocardial infarction in analyses adjusted for socioeconomic factors with follow-up from 1960 to 1992. This study was a re-analysis of a former study of mortality in this cohort (81). The studies published so far (9, 80, 81, *study II*, *study VIII*) and another Swedish study with overall negative results for increased mortality from myocardial infarction in association with occupational exposure to ELF EMF [unpublished manuscript of Ahlbom A, Feychting M, Gustavsson A, Hallquist J, Johansen C, Kheifets L, et al (No association between occupational magnetic field exposure and myocardial infarction incidence in the SHEEP study)] provide no indication of

Table 8. Relative risk (RR)^a for a pacemaker implant among 24 056 men employed for at least 3 months in a Danish utility company, 1900–1993, by average estimated level of exposure to electromagnetic fields (EMF), as adjusted for age, calendar year and duration of employment. (95% CI = 95% confidence interval)

EMF exposure	Pacemaker implantation	
	RR	95% CI
Background ($\leq 0.09 \mu\text{T}$) (N=20)	1.0	-
Medium (0.1–0.99 μT) (N=61)	1.06	0.60–1.87
High ($\geq 1.0 \mu\text{T}$) (N=23)	0.89	0.50–1.63
Unknown (N=31)	1.06	0.61–1.87

^a From a Poisson regression model with the variables occupational exposure to EMF, age, duration of employment, and calendar year as covariates (P for trend 0.7).

an association between this exposure and the risk of cardiovascular disease.

Exposure to radiofrequency electromagnetic fields and risk of cancer

Overall, 2876 cases of cancer were reported among male mobile telephone subscribers, with 3328 expected, yielding a decreased SIR of 0.86 (95% CI 0.83–0.90). The estimate for women was 1.03 (95% CI 0.95–1.13) based on 515 observed cases. There was no evidence of an increased risk of tumors of the brain or nervous system or for salivary glands or leukemia. Of the 154 reported cancers of the brain and nervous system, 144 were situated intracranially. Significant standardized incidence ratios were not found for any subtype or any anatomic location, including the occipital lobe, which would be closest to the antenna of a mobile phone when in use (table 9).

During the period 1943–1996, the mean number of incident cases of ocular malignant melanoma in each 5-year calendar period increased from approximately 30 to 60; however, the age-standardized incidence rates

Table 9. Standardized incidence ratios (SIR) and 95% confidence intervals (95% CI) for intracranial central nervous system tumors categorized according to ICD-O morphology and topography codes among 420 095 cellular telephone subscribers in Denmark, 1982–1996.

Morphology	Observed ^a (N)	Expected ^a (N)	SIR	95% CI
Glioma (191.0–9) ^b	66	70.2	0.94	0.72–1.20
Cerebrum (191.0)	15	17.4	0.86	0.48–1.42
Frontal lobe (191.1)	19	17.0	1.11	0.67–1.75
Temporal lobe (191.2)	11	12.8	0.86	0.42–1.54
Parietal lobe (191.3)	5	10.5	0.48	0.15–1.11
Occipital lobe (191.4)	5	2.8	1.79	0.58–4.17
Cerebellum (191.6)	1	0.6	1.67	0.04–9.29
Other and unspecified (191.5; 191.7; 191.8; 191.9)	10	9.1	1.10	0.52–2.02
Meningioma (192.1) ^c	16	18.6	0.86	0.49–1.40
Meninges	..	..	..	..
Nerve sheath tumors (192.0) ^d	7	10.9	0.64	0.26–1.32
Cranial nerves	..	..	..	..
Other and unspecified (191.0–191.9; 192.0; 192.1; 194.3; 194.4) ^{e, f}	55	42.1	1.31	0.98–1.70

^a Topography code in parenthesis.

^b ICD-O morphology codes: 93800–94603 [except 93923]; 94403–94423; 94013; 93841, 94000–94003, 94103–94213, 94500–94513.

^c ICD-O morphology codes: 95300–95393.

^d ICD-O morphology codes: 95400–95700; including acoustic neuromas.

^e ICD-O morphology codes: 80000, 80001, 80003, 80500, 91200–91611, 93501, 93611, 93923, 94703, 94713, 94723, 94733, 94903, 95003, 95013, 95033, 95060, 99900, 99901, 99903, 99900, 99990, 99993.

^f Includes pituitary gland tumors (of which there were four craniopharyngiomas) and pineal gland tumors (of which there were two).

remained fairly stable, with only small, irregular changes between 0.61 and 0.79 per 100 000 per year, consistent with values reported in other countries. In figure 2, the incidence rate is contrasted with the exponential increase in the number of subscribers to mobile telephones in Denmark between 1982 and 1996.

The mobile phone is penetrating everyday life and activities at a speed of 1 million new customers every month worldwide. A possible association between the use of mobile phones and the risk of cancer was investigated in two prevalence case-control studies in Sweden (82–85), three hospital-based incidence case-control studies in the United States (86–88), one population-based incidence case-control study in Finland (89), and two cohort studies in the United States (90, 91) and Denmark (*study V*). No significantly increased overall risk of brain tumors was identified in these studies, and a comparison of the results of these studies excluded relative risks greater than 1.2–1.3 (92). One study of occupational exposure has been conducted to date that dealt directly with exposure to RF EMF from wireless communication technologies. Consistent with the results of the Danish cohort study, no association was found between this exposure and cancers of the brain and nerv-

ous system or leukemia among 195 775 workers employed during 1976–1996 in the manufacture and testing of cellular telephones (93). Furthermore, no biological mechanism has been established. RF signals from mobile telephones are not directly genotoxic and are unlikely to act as initiators. If these fields were carcinogenic, they would act as promoters for tumor growth (12), but no convincing evidence for such activity exists in the scientific literature, and a tumor promoting effect would have been revealed in the studies conducted so far (92).

Several rare cancers were studied in two incident case-control interview studies (94). One of the studies reported a fourfold increased risk of ocular melanoma cancer on the basis of 12 exposed persons who reported “probable or certain exposure to mobile phones”. In an accompanying editorial, it was postulated that, if mobile phones increased the relative risk of uveal melanoma by a factor of four, increases in the incidence over time should be observed (95). In the Danish cohort study (*study VI*), eight cases were observed compared with 13.5 expected (SIR 0.59, 95% CI 0.25–1.17), and in the study (*study VI*) of the incidence rates of malignant melanoma of the eye with the number of mobile phone subscribers, no support for this hypothesis was found.

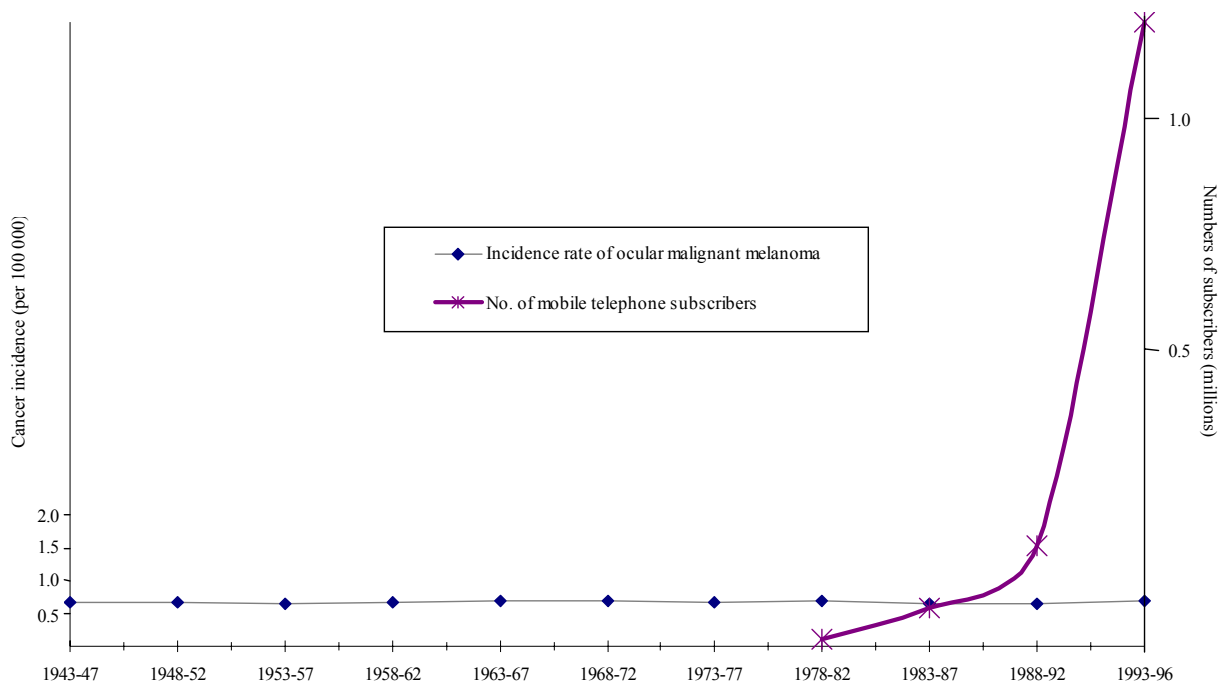


Figure 2. Age-standardized (world standard population) annual incidence (cases per 100 000) of ocular malignant melanoma in Denmark in 1943–1996 and the number of subscribers to cellular telephones in Denmark in 1982–1996.

Discussion

Most of the studies in this thesis were designed as cohort studies, which are generally considered less prone to distortion than even well-conducted case-control studies (96). The cohort design reduces the probability of selection and information biases. Despite the virtual completeness of the cohorts, which were established in a population-based fashion, and the virtual completeness of follow-up for several diseases based on data in high-quality national administrative registers, some possible limitations to the entire study need careful consideration.

Studies of occupational exposure to extremely low-frequency electromagnetic fields

Cohort establishment

Exposure to ELF EMF varies considerably across industries, but occupations in the utility industry, welding, induction furnaces, and electrified transport have consistently been classified as highly exposed. In a cohort study, the persons who enter the cohort must have been exposed to the factor investigated. This requirement appears to have been addressed by the formation of a national cohort of employees in the utility industry. Some 30% of the Danish cohort had been employed for more than 10 years, and close to 50% had been exposed to magnetic fields of $>0.3 \mu\text{T}$. This exposure level is higher than that to which most other Danes are exposed in the workplace, although all people living in the country are exposed, to a certain extent, during daily activities (14). Furthermore, an exposure gradient was observed within the cohort (*study I*).

Selection bias

This manner of establishing a cohort cannot secure the inclusion of all employees in the utility industry during the period of study. The results would be biased if one of the diseases of interest were diagnosed more or less frequently among employees not included in the cohort than among employees who entered the cohort. Healthy persons tend to become and remain employees, whereas those who are less healthy remain unemployed, are disabled, or retire. This "healthy worker" effect may lead to negative results because few members in the cohort develop one of the diseases studied. A systematic

pattern of reduced risk of all cancers, cause-specific mortality, neurodegenerative diseases, or arrhythmia-related heart disease was not observed, however, among the cohort members when they were compared with the Danish population. In addition this methodological problem was addressed in analyses of groups of employees characterized by different levels of the exposure to ELF EMF in relation to neurodegenerative diseases and arrhythmia-related heart disease.

There are, however, indications that employees in the utility industry differ from the general population. In *study I*, the observed numbers of some cancers were lower than the expected numbers. For both genders, these cancers included cancers of the buccal cavity and urinary bladder and non-Hodgkin lymphoma. The presence of one or more selection factors may explain these results.

The persons with ALS or other neurodegenerative diseases included only hospitalized cases. Therefore, the possibility exists that some cases may have been diagnosed outside a hospital (eg, by a general practitioner) and were consequently not reported to one of the registers. This problem might have been serious in *study IV*; however, it can be anticipated that persons with these neurodegenerative disorders are hospitalized at least once. ALS is a rare, fatal neurodegenerative disease (patients can expect to survive only a few years after the date of diagnosis) involving the motor cortex, cerebrospinal tract, and anterior horn cells of the spinal cord, which is characterized by a progressive reduction in muscular function, including the respiratory muscles. In order to survive and cope with the symptoms of ALS, patients must be hospitalized within the first year of diagnosis. Some cases of Alzheimer's disease, senile dementia, demyelinating diseases, Parkinson's disease, cerebral palsy, epilepsy, or spinal medullary diseases may have been diagnosed outside the Danish hospital system, leaving room for more conservative estimates of the true relative risks for these disorders in association with exposure to ELF EMF. This consideration would become serious, however, only if the rate of the diagnoses established outside hospitals was higher for the cohort members than for the background population. There is no reason to believe that this event is unevenly distributed among utility workers and the general population.

Pacemakers can be implanted only in highly specialized hospital units, and the Danish Pacemaker Register came into operation when pacemaker implantation was

introduced in Denmark. It is unlikely that Danish patients were treated for arrhythmia-related heart disorders abroad before 1982, and there is no reason to believe that cohort members would have been registered more frequently than the general population.

Misclassification of exposure

In epidemiologic studies, risk estimates close to unity may indicate nondifferential misclassification of the exposure. In occupational epidemiologic studies, detailed measurements are usually impossible, very expensive, or time-consuming. The ideal means for estimating occupational exposure to magnetic fields is to obtain individual data on the exposure of each study participant from long-term measurements. The main concern with the use of a JEM in epidemiologic studies is the introduction of nondifferential misclassification of exposure. Nondifferential misclassification may bias the risk estimate in any direction and even reverse a dose-response pattern (97, 98). In studies that include more than two exposure levels, the misclassified odds ratio for the most extreme exposure categories would be biased toward the null, but odds ratios for intermediate levels of exposure would be biased away from the null (99). In these simulation studies, such bias appeared to be restricted to situations of multiple categories of exposure and a high degree of misclassification mainly between the two extreme categories (97, 99, 100). In most situations, misclassification occurs mainly between adjacent categories of exposure, and Marshall (100) showed that even 50% misclassification from each exposure category to each adjacent category would not mask a substantial risk increment. Unfortunately, all these studies addressed a situation in which the actual exposure was exhaustively identified by category when correctly classified. In contrast, actual exposure to magnetic fields can vary considerably even within correctly classified categories. This variation may result in bias in both directions. On one hand, the categorization in itself corresponds to a kind of misclassification, assuming no variation in exposure within categories. On the other, the true importance of misclassifying an observation from the upper end of a category to the lower end of the succeeding category is negligible.

The use of several different exposure measurement protocols in occupational studies of the association between occupational exposure to ELF EMF and risks of disease, including mean exposure, peak exposure, or exposures above a certain threshold, has made it difficult to draw conclusions about the association. Some of the largest studies of utility workers (49, 81, 101) found that estimating past exposure to ELF EMF from current monitoring was less of a problem than for other occupational exposures. A review of job histories in one of these

studies (49) showed that the correlations between indices based on the last job and on all jobs varied between 0.75 and 0.78. The mean was slightly lower when only the last job was used. The last job was particularly useful for identifying the most highly exposed people (for the 90th percentile exposure cut-off point for the last job and for all jobs, sensitivity = 0.69, specificity = 0.97, kappa = 0.66). The results suggest that, although not all workers starting in highly exposed jobs stayed in them, workers who ended their worklife in highly exposed jobs had stayed in these jobs throughout their worklife (102).

A comparison of the Danish JEM with measurements of exposure to magnetic fields in utility industries showed consistency at the level of the four general categories of expected exposure to magnetic fields in the JEM (103). The validation study (*study VI*) was conducted to compare the JEM-assigned exposure and 8-hour measurements conducted by Skotte (14). In this study, some misclassification of a categorized exposure to magnetic field was observed when the JEM was used. Most of the misclassification occurred between adjacent categories of exposure. Thus the distribution of measurements of exposure to magnetic fields was similar for workers in the medium and high categories, but the JEM truly separated low and very highly exposed workers in the two extreme JEM categories. On the basis of these results, the exposure categories were grouped as background exposure ($\leq 0.09 \mu\text{T}$), medium exposure ($0.1\text{--}0.99 \mu\text{T}$), high exposure ($\geq 1.0 \mu\text{T}$), and unknown exposure. This new JEM was used in *study VIII*. A comparison of the four exposure category-specific risk estimates for leukemia, brain tumors, and breast cancer among women applied in *study I* did not show a systematically increased relative risk in the very high exposure category versus the low exposure category.

In conclusion, the job histories of all the utility workers could not be ascertained precisely, and the construction of the JEM was based on general expectations of the exposures in given combinations of job titles and workplaces in combination with previous measurements for members of the cohort. Thus there may have been some nondifferential misclassification of the exposure variable. The JEM-assigned exposure separated truly low and very highly exposed workers, however, and is superior to exposure assessment in census studies, information on occupation from death certificates, and other types of routinely collected information on occupation.

Misclassification of the outcome

The data sources used for follow-up in these studies were public registers kept for administrative purposes, and data on the outcome of interest in each of the studies were collected independently of the hypotheses

investigated. These latter data are of high quality. Registration in the Danish Cancer Register (*study I*) is based on notification forms that are filled out by hospital departments and practicing physicians whenever a case of cancer is diagnosed or found at autopsy and whenever there is a change in an initial diagnosis. The cases recorded manually are supplemented by unrecorded cases found by computerized linkage to death certificate files and the National Register of Patients (45). The entire process is supervised by physicians. Ambiguous or contradictory information, either within a notification form or between forms, leads to queries for approximately 10% of the notifications received. Comprehensive evaluation has shown that the Register is 95–99% complete and valid (104–107).

Causes of death are notified by the National Board of Health (*study II*) in a continuous linkage procedure with the Central Population Register. This register is considered to be 100% complete; however, causes of death for former Danes who become citizens of other countries or disappear are not notified to the register (108). Apart from death from cancer, the diagnosis stated as the cause of death has low validity because autopsy rates have been declining, from 45% of all deaths in 1970 to 12.5% in 1996. Cardiovascular disease is stated as the cause of death in many cases, without any reliable clinical information or confirmation by autopsy (109).

The Danish National Hospital Register has collected nationwide data on all somatic hospital admissions since 1977 (*study IV*). Nearly complete registration of somatic hospital events in Denmark is combined with ideal conditions for long-term follow-up. The Register is appropriate for surveying the occurrence of diseases. The general validity of the Register is considered to be high (110). In *study II*, the medical records for all 14 cases of ALS were obtained from neurological departments. This review confirmed the diagnosis. In *study IV* the medical records of all 20 patients discharged with a motor neuron disease from neurological departments were reviewed, and this review revealed 15 patients with a diagnosis of ALS. Four patients who received an initial diagnosis of motor neuron disease were later found to have ALS, and the last patient received a diagnosis of nonspecific motor neuron disease (ICD-8 348.99).

The degree of completeness of the Danish Multiple Sclerosis Register (*study III*) has been estimated to be some 90% (44).

The population-based Danish Pacemaker Register (*study VIII*) was established in 1982. Since its inception, all the data have been validated and are considered 100% complete (46).

The use of population-based nationwide registers of morbidity improved the quality of the majority of cohort studies in the present thesis over that of studies

based on mortality rates. The low frequency of autopsy, which validates the cause of death stated on a death certificate, illustrates why studies of cause-specific mortality have more of a hypothesis-generating nature. The discrepancy between cause of death as stated on a death certificate and that defined by autopsy may bias information on the outcome in both directions. It is well known that some causes of death are overreported and others underreported (108, 109, 111), making it almost impossible to draw etiologic conclusions on the diseases included in the present thesis from death certificates.

Confounding

An association was found between exposure to ELF EMF and the risk of ALS. This association may be confounded by electric shocks, which may be closely related to the strength of the EMF and also to the outcome. It was not possible to adjust for this confounder because information could not be obtained on exposure to this factor. No other occupational factors have consistently been associated with an increased risk of ALS. It was not possible to obtain information on exposure to other occupational factors at the workplace, except asbestos. Exposure to asbestos was included, as earlier studies of utility workers had shown an increased risk of lung cancer. The present results also showed that the employees with high exposure to asbestos were at a higher risk of lung cancer and pleural cancer than those with low exposure. In the initial phase of the study, the possibility was explored of obtaining information on exposure to solvents and pesticides, which have been claimed to cause brain tumors, but the results were disappointing.

No information was available on other exposures or life-style factors associated with the diseases, such as lack of physical activity, poor diet, alcohol consumption, or cigarette smoking. For both genders, the risk of lung cancer was higher than expected; however, it is not clear whether this increased risk was due to above-average exposure to asbestos, an increased prevalence of smoking, or a combination of the two. Although mortality data are of limited validity (108, 109), the mortality rates from acute myocardial infarction and alcoholism among men in the cohort were as expected (*study II*). The overall increase in the mortality rate by increasing level of exposure to EMF was confined mainly to causes of death that are associated with tobacco smoking (lung cancer, pleural cancer, cardiac arteriosclerosis, bronchitis and emphysema). Therefore it is possible that confounding by tobacco smoking was the cause of the increased mortality rates observed for these causes. The cause(s) of MS seem(s) consistent with an environmental effect occurring on a background of genetic susceptibility. In *study III*, the results did not indicate that EMF are an environmental agent that plays a

significant role in the causation of MS. Residual confounding by other suspected risk factors for MS prevalent among utility workers cannot be excluded; however, it would be difficult to identify such factors (112).

Chance

The possibility can never be excluded that positive results obtained in a study are due to chance. The statistical models were chosen before the mortality study was conducted (*study II*). Naturally, the statistical models evolved over the years of study, and the later papers included both external and internal comparisons. The finding of an increased risk of ALS in the cause-specific mortality study was a posteriori (*study II*) and generated a hypothesis that was confirmed in the morbidity study (*study IV*). The finding of an increased risk of ALS agreed with the results of several other studies with cohorts of utility workers or workers otherwise exposed to electricity (65–70, 72–74, *study I*).

Analyses

The data from each of the cohort studies were analyzed by calculating the standardized incidence ratio, which is customary in register-based cohort studies with rare exposures. When disease rates on the general population are used to calculate the expected number of cases of a disease in a given cohort, the incidence rates may be influenced by the disease rates in the cohort under study to a certain degree because the observed cases of the disease among the exposed cohort members also contribute to the numerator of the population rates used to calculate the expected number of cases. This influence is of minor importance if the number of outcomes among members of the cohort is smaller than in the general population. The degree to which standard incidence ratios are underestimates of the true relative risk depends on (i) the proportion of exposed persons in the population and (ii) the absolute difference in the incidence of the outcome among exposed and unexposed persons (113). In the Danish population 0.23% of the population is exposed in their homes to magnetic fields in excess of 0.25 μT , and 0.06% are exposed to 0.4 μT (7). Utility employees can be considered to be the largest group occupationally exposed to ELF EMF; however, welders, electricians, and engine drivers are also exposed to this agent at higher levels than other occupational categories or than in residential exposure. In the various periods of study, the cohort members in *studies I–IV* and in *study V* developed several disorders, including cancer, ALS, and arrhythmia-related heart disease, and these disorders represented less than 1% of the cases occurring in the general population in the same period. In conclusion, the relative risk estimates calculated

by use of the standardized incidence ratio, although slightly conservative, appear to reflect the true relative risk. It is unlikely that the number of cases of each outcome among the cohort members influenced the comparisons with the general population to any meaningful degree.

Studies of radiofrequency electromagnetic fields and risk of cancer

Most of the methodological comments on the two studies of exposure to RF EMF and the risk of cancer were addressed in the previous sections, including cohort establishment, selection bias, misclassification of exposure and outcome, confounding, and analyses. Two additional comments must be added.

Although the large cohort study of mobile phone subscribers (*study V*) had clear advantages, it also had several limitations. Selection bias could not be excluded, since all the corporate users were excluded and they may have been heavy users. The analyses showed a significantly reduced standardized incidence ratio for lung cancer among men; this finding indicated a lower frequency of smoking in the cohort than in the population. Although smoking is not a risk factor for brain cancer, the SIR analyses were not sufficient to address the question without the inclusion of adjustment for smoking and socioeconomic factors, and such adjustment was not possible. This bias was partly addressed in analyses of various groups of users by latency, duration of use, age at first subscription, and mobile phone system used. These analyses supported the estimates obtained with the SIR analyses. Furthermore, the information on exposure did not allow separate estimates for tumors in the anatomic areas of the brain that were considered to be highly exposed to RF fields. Exposure was based on subscription dates only, leaving room for misclassification. The exposure assessment included no information on possible occupational or life-style factors suspected to be associated with the risk of cancer. These methodological questions were also addressed in two comments to *study VI* (114, 115).

In the cohort study (*study V*), the risk of ocular cancer was 0.59 (95% CI 0.25–1.17) on the basis of eight observed cases, and this result was further evaluated in a comparison of the incidence of ocular malignant melanoma with the change in the number of mobile phone subscribers over 15 years of observation (*study VII*). This data set was established on the basis of a sample from the Danish Cancer Register, and there is no reason to believe that differential reporting of this tumor could explain the very stable incidence rates observed over nearly 50 years of registration. In general,

incidence studies can only establish the absolute numbers of cancers by topography and morphology, and these numbers can be used to calculate incidence rates over time by calendar period, age, and gender. This type of study may be viewed as hypothesis-generating since no information on possible risk factors is included in the Danish Cancer Register, apart from date of diagnosis, age, and gender. Despite these limitations, the results largely confirmed the findings of *study V*.

Causality

The observations made in these studies can be used to evaluate the extent to which EMF cause disease. Hill (116) listed nine standards to help determine in what circumstances one can pass from the observation of an association to a verdict of causation. He suggested that the following issues be considered in distinguishing association from causation: strength, temporality, coherence, consistency, specificity, biological gradient, strength of association, analogy, and biological plausibility. He stated "None of these nine standards can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*".

In relation to the causation of cancer by ELF EMF the main problem is the lack of a plausible biological mechanism when combined with the very weak risk estimates observed, the possibility arises that some unknown or unmeasured confounder or other source of bias can explain the results. The evaluation of the working group convened by IARC (7) noted that the association between childhood leukemia and high levels of magnetic fields was unlikely to be due to chance, but it may have been affected by bias. Although the evidence for carcinogenicity in humans and animals was evaluated as inadequate in relation to all cancers except childhood leukemia, ELF EMF were evaluated overall as possibly carcinogenic to humans (7). The epidemiologic studies included in this thesis did not support the carcinogenicity of ELF EMF. It is not possible to draw firm conclusions about the relation between exposure to RF EMF and the risk of cancer from the studies conducted so far; however, present knowledge and the standards of Hill (116) indicate that this is unlikely.

The association between exposure to ELF EMF and ALS has not been fully investigated. The most plausible biological explanation is that exposure to electric shocks or to another unknown factor associated with electricity in jobs, which implies above-average exposure to electricity, is the cause. This possibility has not been fully explored in the studies published so far. The hypothetical association with electric shocks is biologically plausible, as shown in several experimental and

epidemiologic studies. The association between exposure to ELF EMF and Alzheimer's disease or dementia is only weak, and the biological mechanism responsible for such associations has not been clarified. There is no reason to believe that exposure to ELF EMF is associated with heart disease, although the initial study by Savitz et al (9) was based on evidence from human experiments (10). Epidemiologic studies published before (*study II*) and after the publication of Savitz et al (9) did not confirm this result [81, *study VIII* and the unpublished manuscript of Ahlbom A, Feychting M, Gustavsson A, Hallquist J, Johansen C, Kheifets L, et al (No association between occupational magnetic field exposure and myocardial infarction incidence in the SHEEP study)].

Future studies

Additional epidemiologic studies designed to address some of the methodological problems in the studies conducted so far may improve current understanding of the role of ELF EMF in cancer etiology. Improved exposure assessments would be crucial in this context, as well as the use of new metrics, such as transients, and the combination of exposures in residential and occupational environments. Definitions of highly exposed groups of employees according to measurement protocols would also improve the overall quality of the studies. Large cohort studies of persons exposed to electric shocks or electroconvulsive therapy could further clarify the etiology of ALS. More experimental laboratory work is needed to clarify the effects of ELF EMF and other characteristics of electricity, such as shock application, transient field exposure, and conductance on nervous tissue.

The few cohort investigations of mobile phones and other devices should be extended (89, 90, 93, *study V*). In addition, studies that include long-term users and heavy users and studies of children would be of interest. Although the ongoing debate concerns a possible association between mobile phone use and cancer, several neurological symptoms and diseases could also be included among the outcomes studied. Improvements in exposure assessment are crucial, but the absence of a plausible biological mechanism for carcinogenic or other effects will make it difficult to establish the relevant dosimetry.

A large case-control study is being conducted in 13 countries, coordinated by IARC; however, such studies are prone to selection and information biases and confounding, and they suffer from the problems of the validity of self-reports of mobile phone use. Care must be taken in the evaluation of individual study results, as

some significant findings may appear by chance alone, due to the multiple comparisons and subgroup analyses conducted within each study.

Concluding remarks

This thesis is based on the results of several cohort studies conducted in Denmark on the possible associations between exposure to EMF and the risks for several diseases. The main finding is that exposure to ELF EMF, electric shocks, or some other factor related to alternating current electricity is associated with ALS, but not

with other neurodegenerative diseases of the CNS, cancer, or cardiovascular disorders. Currently, there is no convincing evidence that RF EMF (mobile phones) are associated with cancer in adults.

The advantages of the studies covered by the present thesis include the establishment of nationwide cohorts, access to population-based databases and almost complete registration of disease, the use of morbidity data as the outcome measure in most studies as compared with mortality, and validation of the JEM developed to assess exposure in five of the studies. An effect of non-differential misclassification, bias, or unknown confounding, separately or in combination, cannot be excluded.

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