THESIS TITLE

# Residential exposure to 60 hertz magnetic fields and adult cancers

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ABSTRACT

This thesis comprises three independent but interrelated manuscripts. (1) The results from seven epidemiological studies of adult cancers in relation to residential exposure to power frequency magnetic fields (MF) indicated that the association between leukemia and MF has been inconsistent. It also indicated that the risks of brain tumors and breast cancer, the other cancers frequently suspected of being associated with occupational exposure to MF, were rarely investigated. Based on these epidemiological results, the analysis of the roles of chance and bias, and the criteria for causal inferences, it appears that the evidence is not strong enough to support the putative causal relationship between residential MF and adult cancers. (2) A case-control study, using matching on date of birth, sex, and date of diagnosis, was therefore carried out in northern Taiwan to further evaluate the risks of adult (≧ 15 years of age) leukemia, brain tumors, and female breast cancers in relation to residential exposure to 60 Hz MF. Cases were newly diagnosed cancers reported to the cancer registry between 1987 and 1992 and controls were incident cancers from sites other than those previously suspected of being associated with MF during the same period. Assessment of MF in the residences occupied by the study subjects at the time of diagnosis was performed by modeling power information of high-voltage transmission lines. The results were based on the separate analysis of 708 leukemia, 455 brain tumors, and 1,562 female breast cancers. The risk of leukemia for exposure to MF > 0.2 µT relative to the reference level (< 0.1 µT) was significantly elevated (odds ratio = 1.51, 95% confidence interval 1.05-2.19). A dose-response relationship showed a gradient increase in relative risk estimates for leukemia with MF. The relative risk estimates for brain tumors and female breast cancers were slightly elevated, but were statistically compatible to null. (3) To validate the residential MF estimated from power information, indoor MF of 407 residences occupied by a sample of study subjects at the time of diagnosis were selected and assessed by short-term on site measurements and by modeling concurrent power information. The analysis showed that the measured MF tended to be higher than the estimated MF for most residences, especially for those with lower measured MF. Two indices of agreement between measured and estimated MFs, intraclass correlation coefficient (ICC) for continuous data and kappa (K) for categorical data with cutoff points of 0.1 μT and 0.2 μT, declined with the distance from the transmission lines. Both indices showed a poor agreement (< 0.5) for the residences located more than 149 meters away from the transmission lines. The ICC and K observed from a reduced sample of 114 residences presumably representative of all residences in the study area with respect to the distribution of residential MF was 0.90 and 0.64, respectively.

## RÉSUMÉ

Cette thèse comprend trois manuscrits indépendants mais inter-reliés. (1) Les résultats provenant de sept études épidémiologiques portant sur la relation entre le cancer et l'exposition résidentielle aux champs magnétiques de 60 Hz (CM) chez les adultes indiquent que le lien entre la leucémie et les CM est inconstant. Ces études démontrent aussi que les risques de cancer du cerveau et du sein, deux autres cancers qui sont fréquemment associés à l'exposition aux CM au travail, n'ont pas été étudiés. Les évidences accumulées lors de ces études épidémiologiques, lors de l'analyse du rôle du hasard et des biais et lors de l'étude des critères d'inférence causale ne permettent pas de supporter une relation putative de cause à effet entre l'exposition résidentielle aux CM et le cancer chez l'adulte. (2) Une étude cas-témoin, appariée pour la date de naissance, le genre et la date du diagnostic a été réalisée dans le nord de Taïwan pour évaluer les risques d'une leucémie chez l'adulte, d'une tumeur au cerveau chez l'adulte (15 ans ou plus) et du cancer du sein chez la femme en fonction de l'exposition résidentielle aux CM de 60 Hz. Les cas étaient des cancers nouvellement diagnostiqués et reportés au registre des cancers entre 1987 et 1992. Durant la même période, des personnes récemment atteintes de cancers qui n'étaient pas suspectés d'être reliés aux CM ont été choisies comme témoins. L'évaluation des CM à l'intérieur des résidences des sujets étudiés a été faite au moment du diagnostic en modélisant l'information de la puissance des lignes de transmission de haut-voltage. Les résultats proviennent de l'analyse séparée de 708 leucémies, 455 tumeurs au cerveau et 1 562 cancers du sein chez la femme. Le risque d'une leucémie associée à une exposition aux CM de plus de 0,2 $\mu$T était significativement élevé par rapport au niveau de référence qui était de moins de 0,1 $\mu$T (rapport de cotes = 1,51; intervalle de confiance à 95% 1,05-2,19).

Les résultats ont montré qu'il existe une relation positive entre la quantité des $\mu$T provenant du CM et le risque relatif d'une leucémie ("positive dose-response relationship"). Les estimations des risques relatifs d'une tumeur au cerveau et du cancer du sein chez la femme étaient légèrement élevés, mais n'étaient pas statistiquement significatives. (3) Afin de valider la mesure des CM faite à partir de l'information de la puissance, les CM intérieurs d'un échantillon de 407 résidences occupées par des sujets de l'étude ont été mesurés au moment du diagnostic par la méthode de mesure à court terme sur le terrain ("short-term on site measurements") et par la modélisation de l'information de la puissance. Pour la plupart des résidences, l'analyse a démontré que le CM mesuré avait tendance à être plus petit que celui qui était calculé et plus particulièrement pour les résidences où les CM mesurés étaient petits. Deux indices de concordance entre les CM mesurés et calculés, soit le coefficient de corrélation intra-classes (CCI) pour les données nominales et la statistique kappa (K) pour les données catégoriques (coupures à 0.1 $\mu$T et à 0.2 $\mu$T), ont été calculés. Les résultats ont démontré que ces indices diminuaient en fonction de la distance des lignes de transmission. Les deux indices ont démontré qu'il y avait peu de concordance entre les deux méthodes de mesure du CM pour les résidences situées à plus de 149 mètres des lignes de transmission. A partir d'un échantillon de résidences présumé représentatif de la distribution des CM résidentiels de la région étudiée, le CCI a été estimé à 0.90 et le kappa à 0.64.

## PREFACE

According to the specifications of manuscript-based thesis, the five indented paragraphs below should be reproduced in full in the preface of this thesis.

> Candidates have the option of including, as part of the thesis, the text of a paper(s) submitted or to be submitted for publication, or the clearly-duplicated text of one or more published paper(s). These texts must be bound as an integral part of the thesis.
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> If this option is chosen, connecting texts that provide logical bridges between the different papers are mandatory. The thesis must be written in such a way that is more than a mere collection of manuscripts.
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> The thesis must still conform to all other requirements of the "Guidelines for Thesis Preparation". The thesis must include: a Table of Contents, an abstract in English and French, an introduction which clearly states the rational and objectives of the study, a comprehensive general review of the literature, a final conclusion and summary, and a thorough bibliography or reference list.
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> Additional material must be provided where appropriate (e.g. In appendices) and in sufficient detail to allow a clear and precise judgment to be made of the importance and originality of the research reported in the thesis.
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> In the case of manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. Supervisors must attest to the accuracy of such statements at the doctoral oral defense. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers.

Whether power frequency electric and magnetic fields can affect biological systems, or even how much, are not yet fully appreciated. The investigation of biological effects from exposure to electric and magnetic fields is rapidly evolving. Of particular interest during the past 15 years have been the possible carcinogenic effects of magnetic fields (MF) on humans. Concerns and questions about the health consequences of exposure to seemingly ubiquitous MF in the residence, workplace, and elsewhere in the environment are increasingly raised by the scientific community and have brought attention to the public. The debate on the possible malignancy resulting from exposure to MF has initially and often been driven by epidemiological studies in an area in which few relevant laboratory data have been available. At present, the overall epidemiological evidence that occupational or residential exposure to alternating current MF has harmed people is somewhat consistent but not convincing. However, the trend of consistently publicized connections of MF with certain types of cancer unquestionably deserves further epidemiological and laboratory investigations.

This manuscript-based thesis was written to chronologically review previous epidemiological studies concerning MF and human cancers, with a special emphasis upon the causal relation between residential MF and adult cancers. It is also intended to further evaluate, using case-control design, the carcinogenic risks associated with residential MF in adults, which evolved in part from the inadequacy in number of previous residential adult studies. Validating residential MF estimated from high-voltage transmission lines, a method of MF exposure assessment which was occasionally employed in previous studies but has rarely been assessed empirically, was also integrated in this thesis.

This manuscript-based thesis is divided into three sections. The first, "*An Epidemiological Appraisal of Studies of Residential Exposure to Power Frequency Magnetic Fields and Adult Cancers*", provides a review of residential adult studies of leukemia, brain cancer, and breast cancer — three most postulated MF associated cancers. The roles of chance and bias, and the criteria for causal inferences were used to appraise the evidence of causal relationship. The overall evidence from the studies of children and workers also supplements this review. The second section, "*Long-term Residential Exposure to 60 Hz Magnetic Fields and Risks of Adult Cancers in Taiwan*", encompasses three registry-based case-control analyses, which investigated the adult risks of leukemia, brain tumors, and female breast cancer separately in relation to residential exposure to 60 Hz MF. The results from this section are considered complements which enable the scientific community to further conceive the association between MF and human cancers. The third section titled "*A validity analysis of residential magnetic fields estimated from power information of high-voltage transmission lines*" presents the agreement between residential MFs estimated from power information of high-voltage transmission lines and measured by dosimetric instruments among 407 households in northern Taiwan.

## STATEMENT OF ORIGINALITY

This thesis contains no materials which has been accepted for the award of any degree or diploma in any university. Also to the best of my knowledge and belief, this thesis contains no materials previously published or written by another person, except where references are made in the context of this thesis. Additionally, the data included in this thesis were originally collected for the specific purpose of this thesis.

When this project was designed and conducted, the relationship between exposure to elevated MF and human cancers was inconclusive. This thesis was carried out in order to help resolve controversy as to the potential carcinogenic role of MF emitted from transmission lines. To my best knowledge, the materials of the second manuscript of this thesis was the first research designed to examine the *a prior* hypothesis that residential exposure to elevated MF may increase the risk of female breast cancer.

I have done, under the supervision of thesis supervisor and the thesis committee, most of the work on my own at the phases of design, conduct, analysis, and composition of this thesis. However, I shared the most laborious work on the calculation and on site measurements of residential magnetic fields with three colleagues. Dr. Gilles Thériault and Dr. Ruey S. Lin are two co-authors of all three manuscripts. They have contributed valuable corrections and significant comments on the ways of analyzing data and presenting and interpreting the results for these manuscripts.

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*一九九五年冬於加拿大蒙特婁*

TABLE OF CONTENTS AND LIST OF TABLES AND FIGURES

ABSTRACT ..... I

RÉSUMÉ ..... III

PREFACE ..... V

STATEMENT OF ORIGINALITY ..... VII

ACKNOWLEDGMENTS AND DEDICATION ..... VIII

TABLE OF CONTENTS AND LIST OF TABLES AND FIGURES ..... XI

LIST OF FREQUENTLY USED ACRONYMS AND SYMBOLS ..... XIV

INTRODUCTION ..... 1

LITERATURE REVIEW ON THE CARCINOGENIC EFFECT FROM EXPOSURE TO POWER FREQUENCY ELECTRIC AND MAGNETIC FIELDS ..... 3

- Background ..... 3
- Residential Exposure and Childhood cancers ..... 4
- Residential Exposure and Adult cancers ..... 9
- Occupational Exposure and Adult cancers ..... 12
  - *Leukemia* ..... 13
  - *Brain tumor* ..... 23
  - *Breast cancer* ..... 26
- Electric Appliances and Cancer ..... 28
- Epidemiological Evidence ..... 33
- Public Health Implications ..... 38
- REFERENCE LIST ..... 40

OVERVIEW OF STATISTICAL ANALYSIS ..... 49

TITLE OF MANUSCRIPT I ..... 50

- An Epidemiological Appraisal of Studies of Residential Exposure to Power Frequency Magnetic Fields and Adult Cancers ..... 50
- ABSTRACT ..... 50

INTRODUCTION .......... 52
EVALUATION OF FINDINGS FROM STUDIES OF RESIDENTIAL MF EXPOSURE AND ADULT CANCERS .......... 54
DISCUSSIONS .......... 58
THE ROLE OF CHANCE .......... 58
THE ROLE OF BIAS .......... 59
APPLYING CRITERIA FOR CAUSAL INFERENCE .......... 62
CONCLUSIONS .......... 64
REFERENCES .......... 70
List of Tables and Figures .......... 73
Table 1. Summary of methodology of epidemiological studies of residential exposure to power frequency MF and adult cancers. .......... 73
Table 2. Summary of findings of studies of residential exposure to EMF and adult cancers .......... 75
Table 3. Statistical power of studies to detect relative risk of adult cancers for people with elevated exposure to residential MF. .......... 78

TITLE OF MANUSCRIPT II .......... 80

Long-term Residential Exposure to 60 Hz Magnetic Fields and Risks of Adult Cancers in Taiwan .......... 80
ABSTRACT .......... 80
MATERIALS AND METHODS .......... 83
Background .......... 83
Study subjects .......... 84
Assessment of residential MF exposure .......... 87
Validation of estimated MF .......... 90
Potential confounders .......... 91
Statistical Analysis .......... 92
RESULTS .......... 94
DISCUSSION .......... 98
REFERENCES .......... 106
List of Tables and Figures .......... 110
Table 1. Study groups and participants .......... 110
Table 2. The distributions of matching variables and characteristics of districts in the study area in cases and controls by types of cancer. .......... 111
Table 3. Relative risk of leukemia, brain tumors and female breast cancers by

residential MF exposure in the year of diagnosis. .......... 112
Table 4. Age-specific relative risk of leukemia, brain tumors and female breast cancers by residential MF exposure in the year of diagnosis. .......... 113
Table 5. Sex-specific relative risk of leukemia and brain tumors by residential MF exposure in the year of diagnosis. .......... 114
Table 6. Characteristics of study subjects living with different levels MF emitted from transmission lines (N=2,288) .......... 115

TITLE OF MANUSCRIPT III .......... 116

A validity analysis of residential magnetic fields estimated from power information of high-voltage transmission lines .......... 116
ABSTRACT .......... 116
METHODS .......... 120
Study residences .......... 120
Measured magnetic fields .......... 121
Estimated magnetic fields .......... 122
Statistical Analyses .......... 124
RESULTS .......... 126
DISCUSSION .......... 129
REFERENCES .......... 133
List of Tables and Figures .......... 136
Table 1. Distributions of measured and estimated MFs (mG) of 407 residences by lateral distance from the transmission lines. .......... 136
Table 2. Analysis of variance and Intra-class Correlation Coefficients (ICC) by lateral distance from the transmission lines. .......... 137
Table 3. Categorical data of measured and estimated MFs for 407 study residences with cutoff points of 1 and 2 mG by lateral distance from the transmission lines. .......... 138
Table 4. Kappa (K) for each category of Table 3 .......... 139
Table 5. Weighted Kappa (K*w*) for each category of Table 3 .......... 140
Figure 1.Deviation of estimated MF from measured MF .......... 141

CONCLUSION AND SUMMARY .......... 142

APPENDIX: FORMULA FOR CALCULATING MAGNETIC FIELDS OF POWER LINES WITH SPECIFIED CURRENT .......... 146

## LIST OF FREQUENTLY USED ACRONYMS AND SYMBOLS

Symbols and unit abbreviations

| | |
|---|---|
| $\mu T$ | micro tesla; 1 $\mu T$ = $10^{-6}$ T (tesla, SI unit) |
| $\Omega$ | ohm, electrical resistance |
| G | gauss, magnetic induction; 1 T (tesla, SI unit) = 10,000 G |
| Hz | Hertz, cycle per second |
| K | kappa |
| kV | kilo volt; 1 kV = $10^{3}$ V (volt, SI unit) |
| Kw | weighted Kappa |
| m | meter(s) |
| mG | milli gauss; 1 mG = $10^{-3}$ G (gauss, SI unit) |
| mm | milli meter; 1 mm = $10^{-3}$ m (meter, SI unit) |
| *p* | probability |
| T | tesla, magnetic induction; 1 G (gauss, SI unit) = 0.0001 T |
| time | sec, second; min, minute; hr, hour |
| V | volt, electrical potential |

Acronyms

| | |
|---|---|
| AML | acute myeloid leukemia |
| ANLL | acute non-lymphoid leukemia |
| ANOVA | analysis of variance |
| CI | confidence interval |
| CKM | circuit-kilo-meters |
| CLL | chronic lymphoid leukemia |
| CML | chronic myeloid leukemia |
| CNS | central nervous system |
| CPHNTU | College of Public Health, National Taiwan University |
| CV | coefficient of variance |
| DF | degree of freedom |

| | |
|---|---|
| DMBA | 7,12-dimethylbenz(a)anthracene |
| DNA | deoxidized nucleinic acid |
| DOH | Department of Health |
| DTSP | Department of Transmission and Substation Project |
| EF | electric field |
| ELF | extremely low frequency |
| EMF | electromagnetic field |
| ICD | International Classification of Diseases |
| ICD-O | International Classification of Diseases - Oncology |
| MF | magnetic field |
| NTUH | National Taiwan University Hospital |
| OR | odds ratio |
| PMR | proportional mortality ratio, proportional morbidity ratio |
| PRITPC | Power Research Institute, Taiwan Power Company |
| RDD | random digit dialing |
| RR | relative risk |
| SD | standard deviation |
| SE | standard error |
| SES | socioeconomic status |
| SIR | standardized incidence rate |
| SMR | standardized mortality rate, standardized morbidity rate |
| VHCC | very high current configuration |
| VLCC | very low current configuration |

# INTRODUCTION

Electric power is a product of modern civilization and a familiar miracle to human beings. Generations have come to take for granted the simple flip of a switch that turns night into day. Some serious health consequences of electric shock caused by electric power have been well recognized by the public. In more than a decade, a controversial question has emerged as to the electric power we all depend on: *Does it cause cancer?* The potential biological and human health effects, especially human cancers, have become an issue of scientific debate and public controversy following the stimulus by Wertheimer and Leeper's epidemiological study in 1979. Some subsequent epidemiological studies have supported the results from Wertheimer and Leeper's study, suggesting a link between exposure to power frequency magnetic fields (MF) and certain types of cancer, primarily leukemia and brain tumors. Other studies, however, have found no such a link. In recent years, some epidemiological studies have further suggested a possible association between MF and breast cancer, a common female malignancy in developed countries. This new public health issue has obviously emerged from the epidemiological evidence and will faster more discussions in the future. In addition to epidemiologists, laboratory researchers have been trying to figure out how such an association is biologically plausible and to clarify the specific role, if any, of MF in the causation of human cancers. At present, epidemiological and laboratory studies brought no convincing scientific evidence to show a causal link between MF and human cancers except an agreement that better information is needed. At this stage, an increased conflict between public and electric utilities over the sitting and installation of new transmission and distribution lines as well as other power facilities has turned the essence of this scientific issue into a social and economic problem.

It is not wise to assign a low priority to an issue that could ultimately prove to be a significant public health problem.

The present thesis first reviewed chronologically the epidemiological studies with a special emphasis upon the possible causal association of residential MF with certain types of adult cancers. Compared with the studies of workers and children, the studies of adult residents in relation to residential MF have been neither extensive nor consistent in their findings. A case-control study was therefore conducted to evaluate the risks of adult leukemia, brain tumors, and female breast cancers, three cancers frequently suspected of being associated with MF, in relation to residential exposure to 60 Hz MF in order to provide the further evidence and unravel the current uncertainty associated with the power lines.

The primary objectives of this thesis are:

- To appraise the epidemiological evidence concerning adult cancer risks associated with residential exposure to power frequency MF.

- To determine the relative risk estimates of leukemia (ICD-9: 204-208), brain tumors (ICD-9:191) and female breast cancer (ICD-9:174) among adults aged 15 or more in relation to residential 60 Hz MF.

- To assess the validity of residential MF estimated from power information of high-voltage (69/161/345 kV) transmission lines.

# LITERATURE REVIEW ON THE CARCINOGENIC EFFECT FROM EXPOSURE TO POWER FREQUENCY ELECTRIC AND MAGNETIC FIELDS

## Background

It has long been accepted that ionizing electromagnetic radiation, which has the capacity to accelerate electrons in matter, can induce cancer in any organ in which cancer occurs naturally. Epidemiological evidence on the relationship between ionizing radiation and human cancer already existed from the studies of radiation carcinogenesis among survivors of atomic bombs in Hiroshima and Nagasaki, Japan, from studies of radiologists occupationally exposed to ionizing radiation as well as from studies of underground miners exposed to radon gas and its decay products (IARC [1990]). Electromagnetic fields (EMF) with low frequency, on the other hand, rarely come to people's notice except their thermal effect. This is due to the fact that the energy generated by low frequency EMF is too weak to be able to break chemical bonds and show the carcinogenic potential that is possessed by ionizing radiation. However, the potential non-thermal effect posed by non-ionizing EMF, especially by power frequency (50-60 hertz (Hz)) EMF, has recently attracted more and more attentions worldwide. The recent attentions to the potential risk of exposure to power frequency EMF are mostly built upon a series of epidemiological studies following the childhood study by Wertheimer and Leeper in 1979 (Wertheimer and Leeper [1979]). According to the sources of power frequency EMF, decades of epidemiological literature may be broadly summarized into three categories; residential exposure, occupational exposure and electrical appliance usage.

## Residential Exposure and Childhood cancers

The most cited studies of childhood cancers in relation to residential exposure to extremely-low-frequency (ELF) electric or magnetic fields are four case-control studies (Wertheimer and Leeper [1979], Savitz et al. [1988], London et al. [1991], and Feychting and Ahlbom [1993]). Wertheimer and Leeper first raised the possibility that childhood cancers may be associated with residential exposure to elevated magnetic fields. Compared to children residing in residences of low current wiring configurations, they observed a significant excess risk of all cancers, leukemia, and cancers of the nervous system among children whose residences were assigned high current wiring configurations. This initial discovery was partially supported by the later studies by Savitz et al. [1988], London et al. [1991], and Feychting and Ahlbom [1993], which incorporated actual measurements and appropriate considerations of potential confounders.

In addition to external visible features of nearby electric wires, short-term actual measurements were performed in homes occupied by the study subjects (Savitz et al. [1988] and London et al. [1990]). Twenty-four-hour measurements were further carried out in the study by London et al. [1990] in an attempt to reduce the possible fluctuation of magnetic fields within a day. Both studies reported a 50%-70% increase in risk of leukemia among children living in high-current-configurations homes, which was less than a 2.5 fold increase in risk found by Wertheimer and Leeper [1979]. Using more detailed categorizations of wiring configurations classifications, both studies showed a statistically significant steady rise of leukemia risks with a more than two-fold increase in risk in the very high-current category.

With respect to brain tumors, Savitz et al. [1988] suggested an approximately two-fold increase in risk among children residing in homes of high-current configuration, which was consistent with the initial finding by Wertheimer and Leeper [1979]. However, Savitz et al. [1988] reported no association of short-term measured magnetic fields with brain tumors. The relative risk estimate associated with magnetic fields greater than two milligauss (mG) was 1.0 (95% confidence intervals (CI) = 0.2-4.8). Interestingly, the study by London et al. [1991] in the Los Angeles area also indicated that the association of childhood leukemia risk with measured magnetic or electric fields (regardless of whether the measurement was on the spot or a 24-hour basis) was clearly less evident than that with wiring configuration. A prompt argument concerning the above findings was that wire configuration might be a better surrogate measure than short-term or 24-hour actual measurements for long-term electric and magnetic fields levels (Savitz et al. [1988], London et al. [1991]). This could be especially true considering short-term measurements are subject to diurnal, weekly, seasonal, and annual variation while wire codes are not. This speculation was partially substantiated by two studies empirically showing that the wire codes of Wertheimer and Leeper index only moderately correlated with short-term actual measurements of household magnetic fields. (Kaune et al. [1987], Barnes et al. [1989]). Thériault [1992] stated in his review that ❬..... *wire code represents a better measure of long term exposure to EMF than instant or 24 hours in house measurements do (which is a reasonable assumption) or wire code is a measure of field parameters (such as high frequency transient, spikes, resonance, combination of earth magnetic - man made magnetic fields, or the angle at which magnetic fields interact with the cell) that have not been measured so far by the use of average electric and magnetic exposure estimates;* .....❭ , which suggested that wire codes might be a better surrogate for the unknown parameters associated with magnetic fields and aetiologically relevant to the risk of cancer. Since there are no empirical data to support the above argument, more efforts must be devoted to solve the mysterious puzzle behind the wire codes.

Using power information of major power lines, Feychting and Ahlbom [1993] calculated residential magnetic fields to be associated with the risk of childhood cancers in Sweden. The relative risk estimate of leukemia for exposure to calculated magnetic fields $\geqq$ 2 mG relative to the reference level (< 1 mG) was significantly elevated (odds ratio (OR) = 2.7, 95% CI = 1.0-6.3). The relative risk estimate was more elevated when the upper cutoff point was shifted to 3 mG (OR = 3.8, 95% CI = 1.4-3.9). A weaker association of spot-measured magnetic fields with the risk of leukemia was noticed in this study. No association, on the other hand, linking calculated magnetic fields and brain tumors or lymphoma was observed.

Three methodological strengths of the study by Feychting and Alhbom [1993] enforced the epidemiological evidence of a link between magnetic fields and childhood leukemia. First, this study has a well-defined study base, which greatly minimized the possibility of selection bias arising from the control-selection procedure. Second, compared to the other surrogate methods (e.g. distance from power lines and wire codes), modeling power information is capable of providing a more direct assessment of magnetic fields. Additionally, the property of magnetic fields also makes it possible to theoretically calculate indoor magnetic fields emitted from external power lines, since magnetic fields are hardly shielded by buildings, electric materials and other objects. Besides, instead of assuming that past exposure was like exposure assessed presently, which is an assumption frequently made by retrospective studies, the calculation of magnetic fields from complete utility records is able to estimate past exposure. Third, the Swedish study had complete information on the residential histories for each study subject which further improved the assessment of long-term residential exposure to magnetic fields.

The other studies (Fulton et al. [1980], Tomenius [1986], Coleman et al. [1989], Myers et al. [1990], Olsen et al. [1993], Verkasalo et al. [1993]) concerning childhood cancers in relation to residential magnetic fields were relatively less informative than those reviewed above. The shortcomings for most of the above studies included the selection of controls, exposure assessment, or an insufficient number of study subjects as detailed in the following.

Fulton et al.'s [1980] study was criticized for suffering from a temporal imbalance in the occupancy date of case and control homes (Wertheimer and Leeper [1980]). It appeared that the proportion of high-current-wiring-configuration homes was higher in earlier years and there was a tendency for control homes to have earlier occupancy dates which tend toward higher wire codes residences among controls. Such an imbalance may have biased the risk estimates downward.

The study by Tomenius [1986] was most notable for its first making use of on site measurements of magnetic fields. The dwellings which were within 150 meters (m) on either side of visible 200 kilo volts (kV) power lines or which had estimated magnetic fields of 3 mG were considered "exposed". The relative risk estimates for children living less than 150 m from 200 kV lines were 1.1 (95% CI = 0.3-4.6) for leukemia and 4.0 (95% CI = 0.9-27.1) for central nervous system (CNS) tumors. The corresponding relative risk estimates based on measured magnetic fields were 0.3 (95% CI = 0.1-1.1) and 3.9 (95% CI = 1.2-17.3). These very unstable relative risk estimates were due to the fact that only 2% of dwellings were classified as "exposed". The author provided no explanations for choosing an exposure cutoff point of 150 m or 3 mG which gave rise to a low prevalence of exposed dwellings.

Coleman et al. [1989] and Myer et al. [1990] used the distance from major power facilities (transformer substations for the study by Coleman et al. [1989] and over-head power lines for the study by Myers et al. [1990]) as well as used modeling load on the lines to assess residential magnetic fields. Using 50 m as a cutoff point, Coleman et al. [1989] reported a relative risk estimate of 1.5 (95% CI = 0.7-3.4) for leukemia, whereas Myers et al. [1990] found that the relative risk estimates were 1.1 (95 CI = 0.5-2.5) for non-solid tumor (including leukemia) and 0.8 (95% CI = 0.4-1.9) for solid tumor (including brain tumors). Both studies claimed that the results remained unchanged when the exposure was characterized by incorporating measures of electricity currents carried by substations and power lines.

The drawback of Coleman et al.'s study [1989] was the inclusion of brain tumors as controls. Because brain tumors were suspected of being associated with magnetic fields by Wertheimer and Leeper [1979] and Savitz et al. [1988] and are not uncommon in children, the potential for an underestimation of true relative risk estimates can be expected. The findings by Myers et al. [1990] cannot be compared directly with the other studies due to the difference in study end-points.

Olsen et al. [1993] assessed historical magnetic fields by calculations of power information of 50-400 kV electrical transmission connections and substations and found a significant association between all major types of childhood cancer combined and exposure to magnetic fields from high-voltage installation of $\geqq$ 4 mG (OR = 5.6, 95% CI = 1.6-19). With the same cutoff point, the elevated relative risk estimates persisted for leukemia (OR = 6.0, 95% CI = 0.8-44), tumors of CNS (OR = 6.0, 95% CI = 0.7-44), and malignant lymphoma (OR = 5.0, 95% CI = 0.3-82). These results were very unstable because the proportion of exposed ($\geqq$ 4 mG) subjects was less than 0.5% in both cases and controls.

To my knowledge, the study by Verkasalo et al. [1993] was the only cohort study among publicized childhood studies. They followed some 140,000 boys and girls residing within 500 m of overhead power lines of 110-400 kV who were considered being exposed to at least 0.1 mG. Over a 20-year period, a non-significantly elevated risk for children exposed to magnetic fields $\geqq$ 2 mG relative to exposure of 0.1 mG - 1.9 mG was observed for nervous system tumors (standardized incidence rate (SIR) = 2.3, 95% CI = 0.75-5.4) and leukemia (SIR = 1.6, 95% CI = 0.32-4.5). Subgroup analyses further noted that the observed association between magnetic fields and nervous system tumors was largely attributable to a significant excess of nervous system tumors in boys (OR = 4.2, 95% CI = 1.4-9.9).

Residential Exposure and Adult cancers

The studies of adult cancers in relation to residential exposure to EMF have been neither as extensive nor as consistent as the childhood residential studies. There have been seven publications in this category (Wertheimer and Leeper [1982], McDowall [1986], Severson et al. [1988], Coleman et al. [1989], Youngson et al. [1991], Schreiber et al. [1993], Feychting and Ahlbom [1994]). The risks of adult leukemia and brain tumors observed from these studies were not consistent mainly on the grounds that the end-points used in these studies varied from all causes of mortality (McDowall [1986], Schreiber et al. [1993]) to acute non-lymphoid leukemia incidence (ANLL) only (Severson et al. [1988]).

Duplicating the method of their 1979 study, Wertheimer and Leeper 1982] reported a significantly elevated mortality risk of all cancers, cancer of nervous system, uterus, and lymphomas among exposed adults. However, adult leukemia was not found to be associated with high-current wire configurations.

Among the studies of cancer incidence, Severson et al. [1988] found that neither were spot-measured magnetic fields nor wiring codes associated with ANLL. On the other hand, Coleman et al. [1989] reported an 1.45 fold increased risk (OR = 1.45, 95% CI = 0.54-3.88) of leukemia among people residing within 100 m of power lines or transformer substations. Coleman et al.'s [1989] results were partially supported by Youngson et al. [1991] who suggested a small association between adult myeloid leukemia and residential proximity to overhead lines or estimated magnetic fields. Living less than 50 m of overhead transmission lines was associated with a risk estimate of 1.2 (95% CI = 0.8-1.9) for adult myeloid leukemia, relative to living $\geqq$ 100 m . The relative risk estimate, using <0.1 mG as reference level, for estimated magnetic fields $\geqq$ 1.0 mG was 3.0 (95% CI = 0.8-10.6). No association of magnetic fields with adult lymphoid malignancies was observed in Youngson et al.'s study [1991]. Although both Coleman et al. [1989] and Youngson et al.'s [1991] studies incorporated a large number of study subjects, it was likely that a small association may have comprised the statistical power and yielded imprecise relative risk estimates.

A recent Swedish study (Feychting and Ahlbom [1994]) showed an elevated, but not statistically significant, relative risk estimate for acute myeloid leukemia (AML) (OR = 1.7, 95% CI = 0.8-3.5) and chronic myeloid leukemia (CML) (RR = 1.7, 95% CI = 0.7-3.8) for people living with calculated magnetic fields greater than 2 mG, compared with people exposed to $\leq$ 0.9 mG. The two relative risk estimates were based on nine and seven exposed cases and both have wide confidence intervals. The relative risk estimates for the chronic lymphoid leukemia (CLL) and CNS tumors were very close to null in this study. Using cumulative exposure during the 15 years preceding diagnosis to associate cancer risks, Feychting and Ahlbom [1994] found that the relative risk estimates of AML and CML were 1.9 (95% CI = 0.6-4.7) and 2.7 (95% CI = 1.0-6.4), respectively, for exposure of $\geq$ 30 mG-years relative to <9.9 mG-years.

Two retrospective cohort studies (McDowall [1986], Schreiber et al. [1993]) provided no evidence to support the link between residential magnetic fields and adult cancers. The almost complete follow-up of the two cohort studies greatly avoided the potential selection bias due to an association of loss to follow-up with both the exposure and the subsequent risk of cancer. However, a small number of deaths from certain types of cancer and inadequate exposure assessment confined the inferences of their results.

The residential adult studies certainly should put more emphases on the confounding effect than the childhood studies do, since adults have a lot more chance of being exposed to certain risk factors for cancers in the environment and workplaces. Age, sex, year of diagnosis (or death), and indices of socioeconomic status (SES) were considered by all studies. With the exception of Severson et al. [1988], none of the adults studies have included information of other known risk factors for leukemia or brain tumors from environmental or occupational sources.

Like residential childhood studies, magnetic fields assessment was also inadequate for most residential adult studies. Comprehensive on site measurements were only performed in the studies by Severson et al. [1988] and Feychting and Ahlbom [1994]. The other studies, on the other hand, used a variety of surrogates for magnetic fields including the distance from power lines, calculated magnetic fields from load on the lines, or wiring configuration to indirectly estimate magnetic fields. It was noted that a complete residential history for each subject was considered by Feychting and Ahlbom [1994], which was considered superior to the other adult studies which assessed one single residence which was either occupied at a reference date (Severson et al. [1988], McDowall [1986], Schreiber et al. [1993]) or a place in which the subject spent most of the time within a specific period before diagnosis (Wertheimer and Leeper [1982]).

Occupational Exposure and Adult cancers

The majority of epidemiological studies are concerned about people occupationally exposed to elevated electric and/or magnetic fields in workplaces. Wertheimer and Leeper [1979] first thought over this issue in the discussion of their paper. It was Milham [1982] who brought this issue to a widespread attention. Elevated risks of malignancies including leukemia, brain tumors, and more recently breast cancer have been suspected of resulting from exposure to EMF in workplaces. Like residential studies, the dosimetry of EMF was rarely performed in earlier occupational studies. Rather, the job-title, a surrogate for EMF in the work environment was frequently used with varying definitions of electric-related workers. The lack of exposure measurements certainly compromised the inference of the results from earlier occupational studies. Moreover, the possible exposure measurement errors may have led to an exposure misclassification and subsequently biased the risk estimates. Another common methodological weakness of earlier occupational cohort studies was the incomparability with respect to risk factors for cancer between exposed and unexposed groups. This was especially a commonplace for proportional incidence (or mortality) studies and retrospective cohort studies using administrative data. These methodological drawbacks have been avoided to a great extent in recent studies which incorporated sound exposure assessment methods, thorough considerations of potential confounders and a careful procedure of selecting study subjects.

*Leukemia*

Milham's study [1982], analyzing all deaths of Washington State male residents 20 years old or older between 1950 and 1979, reported an excess of mortality from leukemia among workers in nine occupations presumably with elevated EMF. Following Milham's study, numerous studies of leukemia mortality or incidence among workers in these occupations provided similar results (Wright et al. [1982], Coleman et al. [1983], McDowall [1983], Flodin et al. [1986], Stern et al. [1986], Cartwright et al. [1988], Pearce et al. [1989], Gubéran et al. [1989], Bastuji-Garin et al. [1990], Gardland et al. [1990], Loomis and Savitz [1990], Juutilainen et al. [1990], Robinson et al. [1991], Tö nqvist et al. [1991], Richardson et al. [1992], Guénel et al. [1993]). Some studies, on the other hand, did not find an elevated risk of leukemia among workers in these occupations (Morton et al. [1984], Calle and Savitz [1985], Olin et al. [1985], Blair et al. [1985], Gallagher et al. [1990], Tönqvist et al. [1986], Linet et al. [1988], Matanoski et al. [1989]).

Among the studies which supported the association between EMF-related occupations and leukemia, a pronounced association between electrical occupations and AML was observed from most of them (Wright et al. [1982], McDowall [1983], Flodin et al. [1986], Stern et al. [1986], Cartwright et al. [1988], Bastuji-Garin et al. [1990], Juutilainen et al. [1990], Tönqvist et al. [1991], Guénel et al. [1993]). Two earlier reviews of publications also came up with similar findings. Savitz and Calle [1987] compiled 11 data sets and concluded in their report that the results for total leukemia show a moderate excess risk (relative risk (RR) = 1.2, 95% CI = 1.1-1.3) for workers in occupations presumed to have elevated EMF exposure. The elevated risk was enhanced for acute leukemia (RR = 1.4, 95% CI = 1.2-1.6) and especially AML (RR = 1.5, 95% CI = 1.2-1.8). Coleman and Beral's review [1988] showed a 20% increase for all leukemia and a 45% increase for AML among "electrical workers".

Instead of studying electrical occupations assembled together, some studies were designed to investigate the leukemogenic risk in relation to some specific occupations or habit-related activities such as underground coal miners (Gilman et al. [1985], Tönqvist et al. [1991]), amateur radio operators (Milham [1985], Milham [1988]), workers involved in electric arc welding industry (Milham [1982], Wright et al. [1982], Morton et al. [1984], Stern et al. [1986], Preston-Martin et al. [1988a), Tola et al. [1988], Tönqvist et al. [1991], Richardson et al. [1992]), and employees from telephone companies (Obrams [1988], Wiklund et al. [1981], Howe and Lindsay [1983]).

Contrasting miners working less than 25 years versus those working 25 years or more, Gilman et al. [1985] found that the duration of employment among underground coal miners was associated with the incidence of leukemia (OR = 2.5, $p<0.05$). Approximately equal contribution was from lymphoid and myeloid leukemia. A similar magnitude of relative risk estimate (standardized mortality rate (SMR) = 2.2, 95% CI = 1.0-4.1) for AML was observed among miners in a cohort study by Tönqvist et al. [1991].

A proportional mortality study of amateur radio operators was initially conducted by Milham (Milham [1985]). It showed a significantly elevated proportion of mortality (proportional mortality ratio (PMR) = 2.81, $p<0.01$) among amateur radio operators in the states of Washington and California between 1971 and 1983. Milham [1988] further followed 67,829 amateur radio licensees in the two states which accumulated 232,499 person-years between 1979 and 1984. The later study found a slightly elevated relative risk estimate for leukemia (SMR = 1.24, 95% CI = 0.87-1.72), with an enhanced risk elevation for AML (SMR = 1.76, 95% CI = 1.03-2.85). Because no actual measurements were employed, Milham's findings should be regarded as a basis that calls for further studies to investigate which hazard, if any, was really responsible for the association of leukemia with this hobby-related activity.

The studies of workers involved in electric arc welding tended to consistently show no excess of leukemia among welders despite that welders are considered being exposed to very high magnetic fields. Two proportional mortality studies (Milham [1982], Wright et al. [1982]), two cohort studies (Morton et al. [1984], Tönqvist et al. [1991]) , and one recent case-control study (Richardson et al. [1992]) all concluded no leukemogenic hazards from welding. Additionally, the risks for neither all leukemia nor any cell-specific leukemia were observed to be associated with welding in the compilation of 11 data by Savitz and Calle [1987]. Another meta-analysis of 15 publications also revealed no excess of leukemia among welders. (Stern [1987]).

The leukemogenic risk of welding was, on the other hand, suggested by Stern et al. [1986]. Stern et al. [1986] studied 24,545 shipyard workers, using nested case-control design, and found that welders underwent an elevated risk of leukemia deaths (OR = 3.19, 95% CI = 1.09-9.37) and a more elevated risk of myeloid leukemia (OR = 6.23, 95% CI = 1.64-23.64). The suspicion of welding's leukemogenic effect was later reinforced by Preston-Martin et al.'s study [1988a] in which a strong association between CML and prior employment as a welder was observed (OR = 25.4, $p<0.01$). As the analysis restricted to subjects whose job title included the word "welder" or "welding", the odds ratio was infinity (15 cases versus 0 controls). Both Stern [1986] and Preston-Martin et al.'s [1988a] studies completely measured and adjusted for other risk factors for leukemia. Nevertheless, it was not possible from these two studies to convincingly point out any specific welding-related hazard responsible for the observed association because on site measurements of EMF for workers were not available.

Telephone operators (Wiklund et al. [1981]), telephone servicemen (Howe and Lindsay [1983]), and telephone linemen (Obrams [1988]) were not observed to have higher risk of leukemia mortality or morbidity. The results from telephone workers studies should be interpreted cautiously because these studies were also subject to exposure measurement errors.

The preceding studies appeared to suggest an association of leukemia with the assembly of electrical workers as a whole. In terms of specific occupations, amateur radio operators and underground miners were reported to be associated with an elevated risk of leukemia. It is not possible, however, to draw any firm conclusion concerning the leukemogenic effect of EMF from the above studies mainly due to methodological limitations. Generally, these studies were unable to provide convincing evidence linking EMF and leukemia, since no actual measurements of electric or magnetic fields were performed. However, the potential measurement error due to the use of "job title" was unlikely to be a valid basis for the argument of spurious associations, since the exposure misclassification resulting from the use of "job-title" was likely to be non-differential (Copeland KT [1977]). In addition to exposure measurement errors, the inadequate assessment of other potential leukemogenic agents in workplaces further complicated the interpretation of the results from these studies. With only few exceptions, most studies were unable to thoroughly considered some known risk factors for leukemia such as organic solvent, ionizing radiation, and pesticides. Due to these limitations, the results from earlier studies should be considered preliminary.

Several occupational studies with improvements in methodology have been accomplished recently. The improvements included on site exposure measurements and an extended consideration of potential leukemogenic agents, which were two major drawbacks of earlier studies.

A nested case-control study within a cohort of 6,221 electric utility workers between 1960 and 1988 in Southern California (Sahl et al. [1993]) first measured magnetic fields in the work environment. The combination of measured magnetic fields with job histories was used to create exposure scores in association with the risk of leukemia. The results from Sahl et al.'s study [1993] provided no support for the association of leukemogenic risks with either job categories or exposure scores. The strength of this study was the first application of dosimetry data to assess occupational exposure to magnetic fields. In addition, a well-defined study base greatly reduced the potential bias frequently resulting from control-selection procedures in case-control studies. The main limitation of this study was its relatively small sample size which included only 17 leukemia among electrical workers.

A community-based case-control study (Floderus et al. [1993]), using cancer register cases and community worker controls chosen from a census survey, reported a significantly elevated risk of leukemia (OR = 1.63, 95% CI = 1.10-2.42) for men whose longest lasting job during the ten-year period before diagnosis was estimated to be $\geqq$ 2.9 mG, relative to men with longest lasting job $\leqq$ 1.5 mG during the same period . Subgroup analyses indicated an enhanced risk for CLL (OR = 3.08, 95% CI = 1.62-5.89). The associations were attenuated when magnetic fields were measured for a high-exposure job ever held during one's lifetime. The known environmental risk factors for leukemia including benzene, ionizing radiation, organic solvent, pesticides, and smoking were measured by questionnaires in this study and were not found to show meaningful influences on the observed associations. Additionally, the study base of this study was not limited to any particular industry, indicating that the study subjects as a whole in principle was a representative sample from all male workers in the study area.

Matanoski et al. [1993] examined the mortality risk of leukemia (excluding CLL) among telephone line workers most of whom were retired. The lifetime exposure score for each study subject was created by a combination of work histories with personal monitoring measurements on each job category. When lifetime exposure scores were based on time-weighted-average mean for each job, workers with scores above the median showed an excess of leukemia compared with workers below the median (OR = 2.5, 95% CI = 0.7-8.6). Lifetime exposure scores based on peak fields were also found to be non-significantly associated with a similar elevated risk of leukemia.

Comparing workers in 9 electrical occupations with workers in 18 non-electrical occupations, London et al. [1994] found that electrical workers were at a slightly higher risk of all leukemia (OR = 1.3, 95% CI = 1.1-1.6), ANLL (OR = 1.2, 95% CI = 1.0-1.6), CLL (OR = 1.3, 95% CI = 1.0-1.8), and CML (OR = 1.3, 95% CI = 0.8-2.1). Measurements of magnetic fields for each occupation showed that magnetic fields exposure was higher among workers in electrical occupations than in non-electrical occupations except electrical engineers, which was consistent with the findings by Flynn et al. [1990]. Individual's exposure was assessed by combining his/her occupation with job-specific measured magnetic fields. A weakly uprising trend in the risk of leukemia per 10 mG increase in average magnetic fields was observed (OR = 1.2, 95% CI = 1.0-1.5), with an enhanced trend for CML (OR = 1.6, 95% CI = 1.2-2.0). The results remained unchanged after adjusting for a complete list of potential occupational leukemogens assessed by the expert judgment.

Thériault et al. [1994] used a case-control design nested within some 230,000 electrical utility employees from three power utilities in Canada and France. Significantly elevated risks of ANLL (OR = 2.41, 95% CI = 1.07-5.44) and AML (OR = 3.15, 95% CI = 1.20-8.27) were observed in workers with cumulative exposure >3.1 micro tesla (μT)-years. The relative risk estimate associated with mean exposure >0.2 μT for ANLL and AML was 2.36 (95% CI = 1.00-5.58) and 2.25 (95% CI = 0.79-6.46), respectively. Compared with the sample size of previous studies, the number of study subjects in this study was relatively larger, allowing more precise relative risk estimates for the analyses of cell-specific leukemia and a trend test of risks across several exposure categories. Taking into account the adjustment for possible temporal changes in magnetic fields on the same work site in the construction of exposure matrices was another methodological strength, which further reduced measurement errors in estimating past exposure.

A nested case-control study was conducted to assess whether exposure to electric and magnetic fields among Norwegian railway workers induced leukemia (Tynes et al. [1994]). Exposure assessments of electric and magnetic fields were based on present measurements and information about job titles, work histories, and job descriptions. Like the study by Floderus et al. [1993], exposure data were obtained from an examination of job histories and on site measurements of work places rather than direct measurements for individuals. Neither were electric nor magnetic fields associated with leukemia in railway workers. A direct comparison of the results from Tynes et al. [1994] with the results from previous studies was not appropriate because of the dissimilarity in exposure characteristics. Instead 50 or 60 Hz, the Norwegian electrified railway lines used EMF with 16⅔-Hz.

The most recent publication which investigated the risk of leukemia in association with magnetic fields was carried out by Savitz and Loomis [1995] who retrospectively followed more than 138,000 male employees from five electric power companies in the US contributing some 2,650,000 person-years over a 36-year period. The exposure matrices used in this study were generally similar to those of previous studies. The risk of leukemia was not observed to be associated with indices of magnetic fields. The only exception was that a significant increase in risk (OR = 2.50, 95% CI =1.08-5.76) of leukemia was observed for more than 20 years of employment as an electrician compared with men working in the same occupation for less than five years. The authors concluded that their study did not support the association between occupational magnetic fields and leukemia.

Thus, some recent studies appeared to show a consistency in the association between occupational exposure to magnetic fields and leukemia ( Floderus et al. [1993], Matanoski et al. [1993], London et al. [1994], Thériault et al. [1994]). The other two studies, however, provided no support for such an association (Sahl et al. [1993], Savitz and Loomis et al. [1995]). There were no obvious explanations to the inconsistent results. It was interesting, however, to note that all of the studies except Matanoski et al. [1993] which supported the leukemogenic effect of magnetic fields used cancer incidence as the endpoint in relation to magnetic fields, whereas two studies with null results used mortality cases. There is a consensus that incident cases are superior to the mortality cases in the evaluation of risk factors for the occurrence of diseases, since mortality risks are determined not only by risk factors for the disease development but also by certain prognostic factors following the onset of diseases. The use of incident and deceased cases would not reach the same risk estimates unless the assumption that all prognostic variables after the onset of diseases are independent of the exposure can be satisfied (Sackett [1979]). It was not clear whether the use of deceased cases was responsible for the null results from the two studies by Sahl et al. [1993] and Savitz and Loomis et al. [1995]. An examination of the distribution of prognostic factors between electrical workers and "unexposed" workers will be helpful to clarify this speculation. Moreover, successful treatments of leukemia will lead to a favorable survival and may have compromised the study sample size for the desired statistical power in the studies using mortality rather than incidence as the study end-point.

Two common criticisms about the validity of earlier studies, exposure measurement errors resulting from using job titles and shared exposure to the other leukemogenic factors in workplaces, were not found to be detrimental from the evidence provided by some recent studies.

The study by London et al. [1993] found that magnetic fields were higher among workers in electrical occupations than in non-electrical occupations, which supported the previous assumption that electrical workers have experienced higher magnetic fields. The studies by Floderus et al. [1993] and Matanoski et al. [1993] demonstrated that the risk estimate of leukemia associated with personal monitoring magnetic fields was larger than that related to job titles only, which suggested that the use of job titles may have caused exposure misclassification and led to an underestimation of relative risk estimates. However, the difference in risk estimates was not substantial, indicating that the exposure misclassification in earlier studies was not serious.

No materially meaningful confounding bias was observed in four recent studies which assessed potential confounding effect of risk factors for leukemia other than EMF (Floderus et al. [1993], London et al. [1994], Thériault et al. [1994], Savitz and Loomis et al. [1995]). These results indicated that electrical workers do not tend to have a higher chance to be occupationally exposed to the other leukemogens.

With respect to the dose-response relationship between magnetic fields and leukemia, the evidence was inconsistent across the studies. Three of them claimed a dose-response relationship (Floderus et al. [1993], Matanoski et al. [1993], London et al. [1994]); but the results from Thériault et al. [1994] did not show clear dose-response trends with increasing exposure. Although earlier occupational studies tended to show a stronger association of AML with magnetic fields, this tendency has not been conclusive. The study by Thériault et al. [1994] did observe an enhanced risk of AML. However, cell-type specific analyses by Floderus et al. [1993] and London et al. [1994] suggested an enhanced risk for CLL and CML, respectively.

*Brain tumor*

The acknowledging evidence to associate EMF with the risk of brain tumors initially derived from several case-control studies (Lin et al. [1985], Thomas et al. [1987], Magnani et al. [1987], Speer et al. [1988], Preston-Martin et al. [1989], Loomis and Savitz [1990]).

Using EMF-occupation linkage categorizations, Lin et al. [1985] reported an approximately two fold increase in mortality risk of glioma and astrocytoma among electrical workers in Maryland relative to the occupational category with background levels of EMF. With analogous but not identical exposure probability categorizations of Lin et al. [1985], a significant excess of glioma mortality (OR = 2.6, 95% CI = 1.2-4.3) and astrocytic tumors (OR = 4.6, 95% CI = 1.9-12.2) in electrical workers was found in the study by Thomas et al. [1987]. Speer et al. [1988] also reported an elevated risk of glioma mortality among workers in the transportation, communication and utility industries (OR = 2.6, 95% CI = 1.2-4.3). The study by Loomis and Savitz [1990] compared men involved in electrical occupations with those in all other occupations and found an unfavorable mortality from brain tumors in electrical workers (OR = 1.4, 95% CI =1.1-1.7). The excess of mortality was especially prominent for electrical engineers and technicians (OR = 2.7, 95% CI = 2.1-3.4), telephone workers (OR = 1.6, 95% CI = 1.1-

2.4), electric power workers (OR = 1.7, 95% CI = 1.1-2.7), and electrical workers in manufacturing industries (OR = 2.1, 95% CI = 1.3-3.4).

In contrast to the findings from the above case-control studies, most cohort studies of brain tumors provided no support for the association between electrical workers and brain tumors (Howe and Lindsay [1983], Olin et al. [1985], Blair et al. [1985], Vågerö et al. [1985], Tönqvis et al. [1986], McLaughlin et al. [1987], Tola et al. [1988], Gubéran et al. [1989], Matanoski et al. [1989], Juutilainen et al. [1990], Tönqvis et al. [1991]). A meta-analysis of eight case-controls studies and ten cohort studies showed that the summarized relative risk estimate from cases-control studies indicated an elevated risk (RR = 1.4, 95% CI = 1.2-1.6) (ORAU [1992]). The results from case-control studies were, however, not homogeneous. On the other hand, the aggregate results from cohort studies showed a null relative risk with a tight confidence interval (RR = 1.0, 95% CI = 0.9-1.1).

Cohort studies are considered to be methodologically superior to case-control studies with respect to the reduction of control-selection bias. However, many occupational retrospective cohort studies of brain tumors have apparently suffered from incomparability between employed electrical workers and general population, a problem that has been well recognized (Wang and Miettinen [1981], Ostlin [1989]), which limited the interpretation of their results. For the similar reasons that earlier occupational leukemia studies were unable to provide sound epidemiological evidence, the earlier occupational studies of brain tumors also failed to provide persuading evidence to substantiate or to oppose the hypothesized linkage between electric or magnetic fields and brain tumors.

Four recent studies which investigated the leukemia risk also examined the potential linkage between occupational exposure to magnetic fields and brain tumors (Sahl et al. [1993], Floderus et al. [1993], Thériault et al. [1994], Savitz and Loomis [1995]). The relative risk estimates of brain tumors were close to one in the study by Sahl et al. [1993]. The studies by Floderus et al. [1993] and Thériault et al. [1994] showed some support for the association of magnetic fields with brain tumors. A 60% increase in risk (OR = 1.63, 95% CI =1.04-2.56) of brain tumors was observed among subjects in the highest quartile of exposure (90th quartile or equivalently 2 mG ) relative to those with exposure ≦ 1.5 mG in the study by Floderus et al. [1993]. Thériault et al. [1994] reported a two fold increase (OR = 1.95, 95% CI = 0.76-5.00) in the risk of brain tumors among men whose cumulative exposure to magnetic fields was above 90th quartile (1.57 (μT)-years). Both studies tended to notice that magnetic fields have a somewhat stronger association with astrocytoma than with the other brain tumors.

The most recent occupational study of brain tumors was conducted by Savitz and Loomis [1995] which reported a link between magnetic fields and brain cancer. The relative risk estimate of brain tumors was highest among workers with a cumulative exposure level ≧ 0.7 μT-years in the two-to-ten-year period before deaths relative to the zero exposure level (RR = 2.56, 95% CI = 1.35-4.86). A relative risk estimate of 1.94 (95% CI =1.34-2.81) was observed for per μT-year increase during two to ten years prior to deaths. When etiologic period was not assumed, the risk of brain tumors increased by an estimated factor of 1.07 (95% CI = 1.01-1.14) per lifetime μT-year increase. A relative risk estimate of 2.29 (95% CI =1.15-4.56) was observed for workers with lifetime occupational exposure ≧ 4.3 μT-years relative to those with lifetime exposure <0.6 μT-year.

The uprising trend in the risk of brain tumors with an increase of magnetic fields was suggested by Savitz and Loomis [1995] and two earlier occupational case-control studies (Lin et al. [1985], Speer et al. [1988]), but was not supported generally by the analyses by Floderus et al. [1993] and Thériault et al. [1994]. Among recent studies designed to examine simultaneously the risks of leukemia and brain tumors, two studies tended to show a stronger association of occupational magnetic fields with leukemia than with brain tumors (Floderus et al. [1993] and Thériault et al. [1994]). The other study showed the opposite results (Savitz and Loomis [1995]).

Given the improvement in methodology, the evidence from recent studies concerning the role of magnetic fields in the occurrence of leukemia and brain tumors needs to be considered seriously. However, any conclusion concerning the causal relationship between occupational magnetic fields and the risk of brain tumors or leukemia at present is believed to be premature.

*Breast cancer*

Laboratory studies have found that the function of pineal gland, an organ in the brain at the roof of the third ventricle, responds to EMF (Bliss et al. [1976], Wilson et al. [1981], Welker et al. [1983]). Specifically, chronic exposure to 60 Hz EMF may suppress the normal nocturnal rise in pineal melatonin in animal models (Wilson et al. [1981], Welker et al. [1983]). These findings led Steven to propose a hypothesis that the use of electric power and subsequent exposure to EMF will increase the risk of breast cancer (Stevens [1987]).

A retrospective cohort study followed 37,952 Norwegian men with occupations potentially exposed to EMF between 1961 and 1985 to evaluate the risk of male breast cancer in relation to occupational magnetic fields exposure. Compared to all economically active men, the cohort experienced a 2.1 fold risk (95% CI = 1.1-3.6) of breast cancer (Tynes and Anderson [1990]). A similar magnitude of relative risk estimate (OR = 1.8, 95% CI = 1.0-3.7) was observed in a case-control study (Demers et al. [1991]) in which self-reported occupations linked to elevated EMF were used to assess the exposure. Another retrospective cohort study (Matanoski et al. [1991]) found zero male breast cancers among New York Telephone Company's line workers, but two central office workers developed breast cancer during the follow-up period (SIR = 6.5, 95% CI = 0.7-23.4). A mortality study (Loomis [1992]) also provided some support for an overall association of electrical occupations with the risk of breast cancer in males (OR = 2.2, 95% CI = 0.6-7.8).

One recent case-control study (Rosebaum et al. [1994]), on the other hand, concluded that no increase in breast cancer risk was observed among male workers presumed to have elevated exposure to EMF (OR = 0.7, 95% CI = 0.3-1.9). Two later studies of active and utility workers have also provided no evidence to support the association between magnetic fields and male breast cancer (Floderus et al. [1993] and Thériault et al. [1994]).

Loomis et al.'s study [1994] was the only publication, to my knowledge, to examine the mortality risk of breast cancer among female electrical workers. Compared to women with other underlying causes of death excluding leukemia and brain cancer, women who died of breast cancer were more frequently employed as electrical workers. After controlling for age, race, marital status and social class, the relative risk estimate for electrical workers was 1.38 (OR = 1.38, 95% CI = 1.04-1.82). The elevated relative risk estimate was enhanced for electrical engineers (OR = 1.73, 95% CI = 0.92-3.25), telephone installer, repairs and line workers (OR = 2.17, 95% CI = 1.17-4.02). The employment of women as electrical workers could be a marker for some risk factors for breast cancer such as higher education level than women in other work forces in general. The education level could be a strong indication of several reproductive factors such as nulliparity, age at first birth, and number of child births. Although the study had indirectly controlled for reproductive characteristics by using broadly defined social class, the possible residual confounding effect due to strong risk factors for female breast cancer, such as reproductive characteristics, could still be responsible for a slightly elevated breast cancer risk (38%) among female electrical workers.

It is fair to say that, unlike leukemia and brain tumors, breast cancer has not been examined adequately with respect to its association with electric or magnetic fields. No appropriate conclusion can be made at present with respect to the hypothesis created by Steven [1987]. Nevertheless, it should be noticed that if the Steven's hypothesis eventually turns out to be true, the risks of the other hormone-dependent cancers such as the cancers of prostate and ovary, and skin melanoma are likely to be affected by EMF as well. Relatively limited epidemiological studies were conducted previously to evaluate Steven's hypothesis (Steven [1987]) or other hormone-dependent cancers.

Electric Appliances and Cancer

The household appliance is a domestic source of electric and magnetic fields. Because household appliances are usually held or located close to or even in contact with the body during usage, the exposure of magnetic fields from certain appliances is greater than that emitted from external power lines. For example, Gauger [1985] reported that the peak magnetic fields for electric razors ranged from low of 60 mG to as high as 20 Gauss (G). A study by Lovely et al. [1994] indicated an average peak magnetic fields for massage units, hair dryers and electric razors of some 3.5 G, 0.3 G, and 1.9 G, respectively. Generally, the appliances generated magnetic fields do not represent significant sources of prolonged exposure in most instances, since they fall off very quickly with distance (Mader and Paralta [1992]). In addition, most of the appliances were not used continuously. However, investigators are still interested in the potential carcinogenic effect of exposure to such intermittent peak magnetic fields.

The electric blanket is the first appliance which has been investigated by epidemiologists. Among childhood studies, Savitz et al. [1990] reported a moderate association of overall childhood cancers with mother's prenatal exposure to electric blanket (OR = 1.3, 95% CI = 0.7-2.2). The associations were prominent for leukemia (OR = 1.7, 95% CI = 0.8-3.6) and brain tumors (OR = 2.5, 95% CI = 1.1-5.5). These results persisted after adjusting for family incomes. This study suggested no association between children's postnatal exposure to electric blankets and childhood cancers.

London et al. [1991] studied the use of appliances during one-year period before cancer diagnosis in relation to the risk of childhood leukemia and found a significantly elevated relative risk estimate for the use of electric hair dryers (OR =2.82, 95% CI =1.42-6.32 ) and black-and-white TV (OR =1.49, 95% CI = 1.01-2.23), but not for the use of electric blanket.

The end-points investigated by four adult studies of appliances usage were diverse

(Preston-Martin et al. [1988b], Verrault et al. [1990], Vena et al. [1991], Lovely et al. [1994]). Preston-Martin et al. [1988b] reported that no elevated risk of myeloid leukemia was associated with electric blanket usage. The relative risk estimate for AML and CML was 0.9 (95% CI = 0.5-1.6) and 0.8 (95% CI = 0.4-1.6), respectively.

Verrault et al. [1990] investigated the risk of germ cell testicular cancer in relation to the previous use of electric blanket among males between 20 and 69 years old. The age-adjusted results showed no association between the cumulative use of electric blanket and germ cell testicular cancer (OR = 1.0, 95% CI = 0.7-1.4). The relative risk estimates were, however, variant for subgroup analyses in which the use of electric blanket was associated with lower relative risk estimate of seminoma (OR = 0.7, 95% CI = 0.5-1.2), but with higher relative risk estimate of non-semino germ cell tumors (OR = 1.4, 95% CI = 0.9-2.3).

In a population-based case-control study, Vena et al. [1990] found null results concerning the use of electric blanket and its potential to increase the risk of post-menopausal breast cancer. Compared to no use, the age and education-adjusted odds ratio for the use of electric blanket in the past ten years of cancer diagnosis was 0.89 (95% CI = 0.66-1.19). A slightly elevated relative risk estimate was observed among those who reported daily use in season, continuously throughout the night for the past ten years (OR = 1.25, 95% CI = 0.73-2.16). These results were not altered after adjustment for Quetelet index and reproductive factors.

A recent study further explored the potential risk of ANLL posed by three motor-driven personal electric appliances (massage units, hair dryers, and electric razor) which may produce more than 5 Gauss at rates-of-change exceeding 100 Gauss/sec of magnetic fields. The ANLL was observed to be positively associated with the use of massage units (OR = 3.00, 95% CI = 1.43-6.32) and electric razors (OR = 1.33, 95% CI = 0.80-2.23). The hair dryers, on the other hand, showed a significantly protective effect against the risk of ANLL (OR = 0.38, 95% CI = 0.22-0.66).

Confounding effects did not appear to be a concern threatening the validity of the above findings, since they were appropriately considered, especially in the studies by Vena et al. [1991] and Lovely et al. [1994].

The exposure misclassification was a likely source of bias in these studies that used self-reported questionnaires to acquire information concerning historical use of electric appliances. The proxy reporting of appliances use for deceased cases (Verrault et al. [1990], Lovely et al. [1994]) enforced the potential for exposure misclassification. All adult studies used community controls (healthy controls) which further increased the potential for recall bias (Linet and Brookmeyer [1987]). An underestimation of relative risk estimates could happen if the exposure misclassification was independent of disease status (Copeland et al. [1977]). The effect of exposure misclassification on the relative risk estimates of these studies can not be judged from the existing information.

Another validity related issue was the control-selection process. Because the study base was not well defined for the above four population-based case-control studies (Preston-Martin et al. [1988b], Verrault et al. [1990], Vena et al. [1991], Lovely et al. [1994]), the possibility of selection bias arising from control-selection process emerged. The controls were recruited from random digit dialing (RDD) (Verrault et al. [1990], Lovely et al.

[1994]), cases' neighbors (Preston-Martin et al. [1988b)), or driver's license rosters and rosters of the Health Care Financing Administration (Vena et al. [1991]). It is agreeable that the appropriateness of RDD may depend on the research questions and the study area. The problem of oversampling people from household with more than one phone and higher socioeconomic status has been recognized in previous studies (Hartge et al. [1984], Greenberg [1990], Olsen et al. [1992]). This problem may have happened to the studies by Verrault et al. [1990] and Lovely et al. [1994] once people from household with more than cne phone and presumably with higher socioeconomic status tend to use appliances more frequently than others. The similar argument may be applied to Vena et al.'s study [1991] in which only people who were listed on the driver's license rosters or rosters of the Health Care Financing Administration were eligible for being selected as controls. Neighbor controls chosen from the case's neighborhood (Preston-Martin et al. [1988b]) were likely to be determined by socioeconomic status and ethnicity. The disadvantage of matching neighborhood was the possibility of introducing selection biases related to the exposure under investigation (Lasky and Stolley [1994]). The real effect of the use of electric blanket may have been masked in Preston-Martin et al.'s study [1988b] due to the similar usage of electric blankets among neighbors.

Due to inconsistent end-points under investigation and possible methodological limitations, the studies of electrical appliances and cancer risks are at a very preliminary stage. The results from these studies should be considered preliminary. Further epidemiological evidence concerning the effect of intermittent exposure to electric or magnetic fields will benefit from the improvement in exposure assessment and from the well-defined study population of future studies.

Epidemiological Evidence

Based on the results from the epidemiological studies published in the past 15 years, the existing evidence, although suggestive, is not strong enough to causally link the power frequency electric or magnetic fields to the risks of certain cancers. Residential studies do suggest associations of indices of household magnetic fields such as wiring configuration and calculated magnetic fields with childhood cancers, primarily leukemia and brain tumors. The association between childhood cancers and short-term on site measurements of magnetic fields, however, is relatively weak. The adult leukemia, but not brain tumors, was also suggested to be associated with the surrogate for magnetic fields. Assessment of EMF exposure was inadequate in general for most residential studies. Although some studies suggested that the use of surrogate for magnetic fields was superior to short-term on site measurements in evaluating long-term residential exposure to magnetic fields, no empirical data so far are available to substantiate this argument. Meanwhile, investigators are also in agreement that the use of surrogate exposure indices is still subject to measurement errors which may led to exposure misclassifications. Because the exposure misclassification encountered by previous residential studies tends to be non-differential, the use of surrogate for actual measurements should not be a valid basis to against the observed associations. In other words, the elevated relative risk, if any, linking EMF to human cancers should be higher than that was derived empirically from past studies (Poole and Trichopoulos [1991]). Nonetheless, a majority of residential studies which used case-control design with undefined study populations were subject to leave some room for control selection biases and possibly cause the results to be upwardly biased. It can be concluded that the residential adult studies were less consistent in their findings than the residential childhood studies.

Occupational studies which investigated carcinogenic effects of magnetic fields from workplaces have contributed to a notable epidemiological evidence. Many earlier occupational cohort studies were based on data collected routinely or for other purposes, which produced possible biasing effects of the "healthy worker" phenomena. Additionally, earlier occupational studies rarely employed actual EMF measurements. These methodological weaknesses had limited control of potential confounding variables and had caused poor quality of exposure information. Given these limitations, little weight can be attached to the findings from earlier occupational studies. A significant improvement in methodology was apparently observed in the recent occupational studies which incorporated on site measurements of EMF and an extensive consideration of potential confounding variables. Generally, recent occupational studies tend to suggest an association of occupational exposure to magnetic fields with leukemia, and to a lesser extent with brain tumors. Although more weights should be given to the evidence from the recent occupational studies, the evidence is still not consistent and convincing enough to argue for the causal relationship between EMF and certain types of cancer.

The occupational studies of breast cancer were less comprehensive than those of leukemia and brain tumors. The occupational studies of breast cancer tend to show an inconsistent link between magnetic fields and the risk of breast cancer among male workers. On the other hand, very few studies in previous years investigated the possible risk of female breast cancer in relation to magnetic fields from home or work environments.

It is fair to conclude that the evidence concerning the role of EMF in the causation of cancers has been enhanced by recent occupational studies with a consequential improvement in their study methods. The overall evidence from both residential and occupational studies, however, is still unable to clarify whether there is an uprising trend in cancer risks with an increase in magnetic fields, i.e., the dose-response relationship. Nor is the evidence able to exactly identify certain cell-specific cancers, if any, most sensitive to the magnetic fields. These uncertainties will remain questionable and arguments for whether magnetic fields are causally associated with human cancers due to magnetic fields will continue with little hope for resolution unless more epidemiological and laboratory investigations can be carried out in the future.

Results concerning household use of particular appliances are difficult to interpret in the absence of a consolidated measure of exposure from all such appliances. Thus, the results from previous studies of cancers in relation to electrical appliances usage should be considered preliminary, and the risk from exposure to pulsed magnetic fields should be further examined in future studies.

There is no doubt that the epidemiological study itself is far less than enough to solve the puzzle concerning the true story between power frequency magnetic fields and human cancers. Specifically, the epidemiological coherence that shows a consistent association of magnetic fields and subsequent risks of cancer morbidity or mortality should be considered an integral part, not the whole, of the causal relationship, if any, between magnetic fields and human cancers. Apparently, the issue of cancer as a consequence of magnetic fields is primarily motivated by the findings from epidemiological studies. To date, laboratory studies are still unable to conclusively provide the evidence pertaining to how magnetic fields interact with biological system and cause cancer. This is mainly due to the fact that tumor production is a complex and lengthy process.

There appears to be an agreement that cancer occurs in stages. A permanent change in the genetic material (DNA) of the cell should be required to initiate the tumor. The initiated tumor will then change and increase in numbers as a consequence of cancer promotion. The two stages usually must occur progressively in the order presented for a tumor to grow and occur. Although there is still no answer today to the mechanism by which magnetic fields interact with the biological system and therefore cause cancer occurrence, it is, however, generally agreed that magnetic fields are unlikely to play an essential role in the stage of cancer initiation, since no convincing laboratory evidence has been able to indicate that magnetic fields cause damage to DNA mostly because of its tiny energy (Easterly [1981], Willams [1984], Hendee and Boteler [1994]).

Rather than playing a role of cancer initiator, the magnetic fields may be involved in the carcinogenesis process by enhancing the growth of initiated cells into clone, escaping from eradication by the immune system, or growing tumor mass. Specifically, magnetic fields are likely to play a role of tumor promoter instead of tumor initiator. To what extent, the magnetic fields are involved in the stages of cancer promotion is unclear. Numerous *in vitro* studies with diverse animal tissues and cultured cells, and *in vivo* studies by animal physiology, behavior, reproduction, growth and development were done in the past, suggesting that the magnetic fields induced changes in biological systems may be manifested at the molecular, cell, organ, and even the whole organism. Some of these changes may be relevant to the pathogenesis process of cancer (Wilson et al. [1990]). The laboratory studies involving lifetime magnetic fields to animals are very limited, giving little data to support or refute the epidemiological findings that magnetic fields are able to cause leukemia or brain tumor.

Thomson et al. [1988] conducted a study in which mice were injected with leukemia cells and exposed to magnetic fields with intensity from 14 mG to 5 G. The results indicated that there was no difference in survival time between exposed and sham exposed groups of animals and concluded that magnetic fields had no influence on the progression rate of leukemia in mice.

Noteworthy magnetic fields effects based on the animal model were found in the area of breast cancer. Leung [1988] demonstrated a subtle increase in the occurrence of breast cancer in rats injected with a known cancer inducing chemical, 7,12-dimethylbenz(a)anthracene (DMBA) and exposed to electric fields. The increase was only observed in number of tumors per tumor-bearing rats; there was no increase in tumors among all the rats receiving electric fields. Consistent results were reported by Beniashvili et al. [1991] and Löcher et al. [1993]. In Beniashvili et al.'s study [1991], female rats exposed to alternating 50 Hz magnetic fields of 20 μT accompanying an initiation with nitrosomethyl urea showed both an increased number and early appearance of mammary tumors. It indicated that apart from increasing the incidence of mammary gland tumors, household low frequency magnetic fields reduced the mean latent period of tumor development and led to earlier predominance of tumors in the exposed rats.

Similar results were observed from a study in which mammary tumors of rats were induced by a carcinogenic chemical, DMBA, and were followed by exposure to homogeneous magnetic fields of 50 Hz, 100 μT, for 24 h/day; 7 day/week for a period of 91 days (Löcher et al. [1993]). The data demonstrated that the exposure of DMBA treated females to alternating magnetic fields of low flux density promoted the growth of tumors and increased the incidence of rats with mammary tumors. These results seemed to have indicated that EMF exposure exerts tumor-promoting effects and substantiated the Steven's hypothesis that exposure to EMF will subsequently cause breast cancer.

EMF's impacts on pineal gland production of the hormone melatonin in whole animals and calcium homeostasis in cellular system are two biological effects of EMF that have been identified and replicated in the laboratory (Blackman et al. [1985], Reiter et al. [1988], Wilson et al. [1990]). Unfortunately, there were very few reliable data for human body bearing directly on how these hypothesized mechanisms are biologically plausible in human body.

Public Health Implications

Because scientists are still debating whether power frequency electric and magnetic fields may produce causal carcinogenic hazards to human health, governments in most countries tend to not set regulations standards for environmental electric and magnetic fields levels or take immediate and immense actions to reduce electric and magnetic fields in the environment at this time (National Institute of Environmental Health Sciences and US Department of Enegry [1995]). However, it would be unwise at this time to conclude that power frequency electric and magnetic fields are not harmful, since their potential for public health impacts could be substantial if the causal relationship between power frequency electric and magnetic fields and certain types of cancer turned out to be real in the future. Previous reviews reported that the relative risk estimates of leukemia, brain tumors, and breast cancer in relation to magnetic fields were in an order of 1.5 to 2.5 (Savitz and Calle [1987], Savitz et al. [1989], Ahlbom [1988], ORAU [1992]). Because of the universe of magnetic fields, an enormous number of cancer incidences can be expected as a consequence of exposure to magnetic fields if the carcinogenic effects of magnetic fields truly existed.

Another issue related to the public health impact is the level for which magnetic fields would produce hazards to human heath. A bunch of epidemiological studies have used 2 or 3 mG as the cutoff point to define broad categories of exposure. Subjects with exposure below this level were considered "unexposed", and above this level were considered "exposed". With this cutoff point, some of these studies do find a significantly elevated risk estimate among those exposed. Despite that, it would be inappropriate to simply treat 2 or 3 mG as a safety threshold, since there is no laboratory evidence for carcinogenic effect at this exposure level. Additionally, the parameters associated with magnetic fields and actually relevant to the occurrence, if any, of cancer are still remaining unclear and undefined, which makes it impossible at present to set any safety threshold for the environmental magnetic fields.

Leukemia and brain tumors are relatively rare in adults, but they are the two leading malignancies among children in most places on earth. In addition, female breast cancer is the top leading female malignancy in developed countries and a cancer that is increasing rapidly in many developing countries (International Agency for Research on Cancer (IARC) [1992]). Given the notable prevalence of leukemia and brain tumors in children and breast cancer in women, it is highly suggested that the issue of EMF and cancer should be an urgent priority for public health administration. Meanwhile, a practice of "prudent avoidance" of prolonged exposure to power frequency electric and magnetic fields is warranted during the period of debate and uncertainty.

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OVERVIEW OF STATISTICAL ANALYSIS

Several statistical methods were employed throughout the contents of this thesis. In the first study which appraised the evidence concerning the risks of adult cancers in association with residential magnetic fields (MF), the meta-analysis, calculating aggregated relative risk estimates by weighting sample size of each study, was used to summarize the relative risk estimates. In the second study which evaluated the risks of adult cancers in relation to residential 60 Hz MF, the odds ratio was used to estimate the relative risk. Crude odds ratios were computed from two by two tables. The adjusted odds ratios, on the other hand, were derived from coefficients of the conditional logistic regression model used for paired-analysis. Confidence intervals were presented to show the magnitude of sampling errors at a 0.95 confidence level. Test for trend of adjusted odds ratios with increase in exposure was performed by examining the significance of regression coefficients for the exposure variable whose levels were considered continuous. Similar methods were used in the analysis of age, sex, and cell-specific risks of adult cancers. The measures of validity of MF estimated from power information included intraclass correlation coefficient for continuous data and kappa for categorical data. Assessments of exact and partial agreements between categorical MFs were performed in the third study. The specific statistical analysis for each individual study was described in some detail in the text of each study with relevant references. The entire analysis was carried out using the computer software package EGRET® (Statistics and Epidemiology Research Corporation, Seattle, WA, 1990) and BMDP New System ™ (BMDP Statistical Software Inc., Los Angeles, 1994).

Title of Manuscript I

An Epidemiological Appraisal of Studies of Residential Exposure to Power Frequency Magnetic Fields and Adult Cancers

ABSTRACT

There have been seven epidemiological studies conducted to evaluate the risks of certain types of cancer among adults in relation to residential exposure to power frequency magnetic fields (MF). Leukemia was observed to be positively associated with MF in three case-control studies. The other two case-control studies and two cohort studies, on the other hand, did not show such a link. Brain tumors and breast cancer have rarely been examined by residential adult studies. Based on the epidemiological results, the analysis of the roles of chance and bias, and the criteria for causal inferences, it appears that the evidence is not strong enough to support the putative causal relationships between residential exposure to power frequency MF and adult leukemia, brain tumors and breast cancer. Compared to the studies of workers and children, residential adult studies have been less comprehensive and less consistent in their findings. Although MF exposure patterns from residential and occupational sources are dissimilar, there is no biological belief at present that these differences may have an impact on the risks of adult cancers. The direct way to answer whether residential exposure to MF is capable of increasing the risks of adult cancers is to conduct additional studies with careful avoidance of methodological flaws. Since breast cancer is prevalent in women and has potential for significant public health impacts, it is especially suggested that future studies should

carefully evaluate the risk of female breast cancer in both workers and residents with elevated MF exposure.

## INTRODUCTION

For more than a decade, a controversial question has emerged about the electric power we all depend on: *Does it have anything to do with cancer?* The potential biological effects, especially human cancer, have become an issue of scientific debate and public controversy following Wertheimer and Leeper's epidemiological study in 1979 [1]. Wertheimer and Leeper's study suggested a link between exposure to power frequency MF and certain types of childhood cancer, in particular leukemia and brain tumors. Some subsequent studies added to evidence supporting Wertheimer and Leeper's findings. Other studies, however, have found no such a link.

Previous studies tended to associate the risk of cancer with either *residential* or *occupational* exposure to MF, and frequently evaluated the risk for children and adults separately. Among *residential* studies, many of them focused on children, some on adults, and only a few on people of all ages. *Occupational* studies, on the other hand, have been conducted among people who have worked in "electrical" occupations. Results from earlier studies have been criticized mainly because of inadequate exposure assessment. Recently, the assessments of MF in residential and occupational settings have been improved by direct measurements. Several extensive reviews of epidemiological studies on the association between cancer and electric and magnetic fields have been published [2-9]. Based on these reviews, there appeared to be a tendency suggesting a moderate association between MF and certain types of cancers, such as acute myeloid leukemia and astrocytic tumors. This tendency is relatively stronger in the studies of children and workers. The studies of adult cancers and residential MF have been neither as extensive nor as consistent as the childhood and occupational studies. This paper reviews residential studies of adult cancers and summarizes the epidemiological evidence from these studies with respect to the causal association between exposure to elevated residential MF and the risk of adult cancers.

## EVALUATION OF FINDINGS FROM STUDIES OF RESIDENTIAL MF EXPOSURE AND ADULT CANCERS

To our knowledge, there have been seven epidemiological studies designed to investigate the risk of adult cancers in association with exposure to residential MF [10-16]. Among them, five were case-control studies [10-14] and two were cohort studies [15, 16]. The study design and exposure assessment methods for each study are summarized in Table 1. The most important methodological feature of these studies was the strategy for assessing residential MF. Wertheimer and Leeper [10], duplicating the methods of their 1979 study, used wire configuration to estimate MF in relation to the risks of adult cancers. The same strategy was used by Severson et al. [11]. Among exposure assessment methods, the distance from power transmission or substation system was frequently used to estimate residential MF [12-16]. The other method of indirect measurements was to calculate MF strength from power load on the external lines [12-14]. Actual measurements of MF at residences occupied by study subjects were performed in only two studies [11, 14]. Instead of measuring the individual residence, actual measurements were carried out in one cohort study to survey the area where the "exposed" group were residing during the follow-up period. [16].

Main findings of the seven studies are summarized in Table 2. Wertheimer and Leeper suggested a significant association between higher current configuration and all cancer combined. Based on the given data in which four exposure levels were defined, the odds ratio (OR) of all cancer mortality for exposure to very high current configuration (VHCC) relative to very low current configuration (VLCC) was 2.18, 95 percent confidence interval (CI) 1.48-3.22. The OR was 1.28, 95 percent CI 1.08-1.52 when only two exposure levels (high current configuration vs low current configuration) were defined. Among studies of cancer incidence, Severson et al. [11] found that neither were spot-measured MF nor wiring codes associated with acute nonlymphoid leukemia (ANLL). On the other hand, Coleman et al. [12] reported a 1.45 fold risk, 95 percent CI 0.54-3.88 of leukemia increased among people residing within 100 meters of power lines. Results from the study by Coleman et al. [12] were partially supported by Youngson et al. [13] which suggested a small association of adult myeloid leukemia (ML) with residential proximity to overhead lines, and a stronger association with estimated MF strength. Living within 100 meters of overhead transmission lines was associated with a relative risk estimate of 1.39, 95 percent CI 0.82-2.53 for adult ML. The relative risk estimate, using $<0.1$ milligauss (mG) as reference level, for MF exposure $\geqq 1.0$ mG was 3.00, 95 percent CI 0.81-11.08. No association of MF with adult lymphoid malignancies was observed. A recent Swedish study by Feychting and Ahlbom [14] showed an elevated relative risk estimate of acute myeloid leukemia (AML) (OR=1.7, 95 percent CI 0.8-3.5) and chronic myeloid leukemia (CML) (RR=1.7, 95 percent CI 0.7-3.8) for people living with estimated MF $\geqq 2$ mG, compared to people exposed to $\leqq 0.9$ mG. The relative risk estimates for chronic lymphatic leukemia (CLL) and central nervous system tumors (CNS tumors), on the other hand, were close to null. The cumulative exposure within 15 years preceding diagnosis was also observed to be associated with the risks of AML (OR=1.9, 95 percent CI 0.6-4.7) and CML (OR=2.7, 95 percent CI 1.0-6.4). The two retrospective cohort studies [15, 16] provided no evidence supporting the hypothesis that MF would increase the risk of certain types of cancer.

With respect to leukemia in general, three case-control studies [12-14] found an increased risk for residential exposure to elevated MF. The elevated risks observed in these studies, however, were not statistically significant. The other two case-control studies [10, 11] and the two retrospective cohort studies [15, 16], on the other hand, found no risk of leukemia for elevated MF in household environment. With respect to the cell-specific risk of leukemia, Youngson et al. [13] linked MF to ML, which was consistent with the findings by Feychting and Ahlbom [14] reporting an equally elevated relative risk specifically for AML and CML, but not for CLL.

An estimate summarizing the magnitude of leukemia risk can be obtained by pooling four case-control studies [11-14] and two cohort studies [15, 16] respectively. The Mantel-Haenszel method [17], using weighted average of the study-specific risk estimates, was used to determine the pooled relative risk estimate for case-control studies. For two cohort studies, the summary estimate was calculated as the ratio between the sum of observed cases and the sum of expected cases derived from the given data, and therefore weighted proportionally to the size of the population for each study [18]. We collapsed exposure into three levels for the summary OR and treated the entire populations that were considered "exposed" in two cohort studies as being exposed for the summary standardized mortality ratio (SMR). The pooled OR for leukemia (including all leukemia and cell-specific leukemia) was 1.01, 95 percent CI 0.77-1.30 for people with moderate exposure. The OR for highly exposed people was 1.17, 95 percent CI 0.90-1.52. For the cohort studies combined, the SMR for the exposed population was 1.15, 95 percent CI 0.57-2.65. An examination of pooled relative risk estimates from both case-control and cohort studies suggested that there is only a slightly elevated risk (some 15 percent) of leukemia for people with exposure to elevated residential MF. However, this weak association was compatible with the null statistically. In addition, caution must be exercised in interpreting the results from this analysis since the methodology was not uniform between the studies [19].

The results from two case-control studies [10, 14] and one cohort study [16] which investigated the risk of CNS tumors were also inconsistent. The study of Wertheimer and Leeper [10] was the only one that reported a significantly elevated risk of CNS tumors (C-ratio = 2.3). The relative risk estimate of the other two studies were either close to one [14] or very unreliably elevated [16]. No elevated site-specific risks of CNS tumors were observed from these studies.

The risk of breast cancer was also studied in one case-control study [10] and two cohort studies [15, 16]. Wertheimer and Leeper [10] reported a significant association between breast cancer and wire configuration. Their findings were not supported by two subsequent cohort studies in which the relative risk estimate for breast cancer was close to one.

## DISCUSSIONS

### THE ROLE OF CHANCE

For each individual study, we calculated its statistical power to reject the null hypothesis of no association. The statistical powers for the main contrasts in each study are presented in Table 3. The power calculation for case-control studies was based on the formula by Schlesselman [20]. The power estimation illustrated by Breslow and Day [21] was used to determine the power for cohort studies. For case-control studies, the prevalence of the exposed population was estimated from the proportion of exposed controls. Only two studies (Coleman et al. [12] and Youngson et al. [13]) had adequate power (0.8) to detect a two-fold risk of leukemia in some of the main contrasts. The study of Feychting and Ahlbom [14] had an adequate power (0.88-0.94) to detect a two-fold risk of CNS tumors, but the power was below 0.5 for detecting a tow-fold risk of AML or CML. The two case-control studies which did not support a link between residential MF and leukemia (Wertheimer and Leeper [10] and Severson et al.[11]) also had inadequate power for the contrast on which the conclusions were based. The power to detect a two-fold risk of leukemia or brain tumors was not reassuring at all for two cohort studies (McDowall [15] and Schreiber et al. [16]) because a very small number of deaths were observed from the "exposed" cohort in both studies. The powers for detecting the risk of breast cancer was 0.97 and 0.59 for the cohort studies of McDowall [15] and Schreiber et al. [16], respectively.

THE ROLE OF BIAS

There are a number of potential sources of bias that could have affected the relative risk estimates in these studies. The discussion will consider three potential sources of bias, i.e., the bias from selection of study subjects in case-control studies or from incomplete follow-up in cohort studies; the bias from exposure assessment of residential MF; and the bias from confounding.

The earlier four case-control studies [10-13] were considered population-based in which cases were identified from regional cancer registry and controls were assembled from non-cancer deaths and neighbors of cases [10], random digit dialing [11], cancer from registry excluding lymphoma and electoral roll [12], or hospitalized patients with non-malignant diseases [13]. Given the quality of cancer registries of the study areas, the likelihood of misclassification of disease should be very small. The selection of controls generally seemed to be appropriate. Healthy controls, likely representative of the population without the cancer of interest, were partially used by three studies [10-12]. Diseased controls were used by three of them [10, 12, 13]. The use of non-cancer deaths [10] or non-malignant diseases [13] was justified by the current knowledge that non-cancer diseases and deaths have not been known to result from MF exposure. The choice of controls in the study of Coleman et al. [12], however, created a potential of spuriously low relative risk estimates because CNS tumors, which have been suspected of being related to MF, were not excluded from the control candidates. Selecting study subjects within a well-defined cohort, the nested case-control study of Feychting and Ahlbom [14] avoided the potential selection bias frequently resulting from case-control studies in which factors associated with both disease and exposure are involved in the selection process of study subjects. The almost complete follow-up of the two cohort studies [15, 16] avoided the potential selection bias due to an association between loss to follow-up and the subsequent risk of cancer. As a whole, one can conclude that there is no indication that selection of study subject has caused a bias in the published study.

Exposure assessment of residential MF was a key issue for the validity of these studies and the inference from their results. The distance to major power facilities, wire configurations, and estimated MF calculated from power load on the lines were the three methods frequently employed by the studies to indirectly estimate residential MF. Actual measurements of MF for each study individual's residence was only conducted in two studies for short-term periods. Although the mechanism by which MF interacts with human body has yet to be fully understood, it is reasonable to assume that a prolonged MF exposure should be required for the subsequent onset of cancer. Given the fluctuation of MF within a day, a month, and a year, the above surrogate methods seem to be more reliable than short-term actual measurements to determine the long-term MF exposure. Because there have been no convincing data available to substantiate this argument, the possibility that the above indirect methods may have produced a misclassification of true exposure at least to some extent should not be completely excluded. Misclassification of exposure may have therefore biased the risk estimates of the above studies. Since the exposure misclassification was likely to be non-differential, the bias due to exposure misclassifications could be a valid rationale for the null findings of some studies [11, 15, 16] but should not be a valid argument against findings from studies which supported the association between MF and certain types of cancer.

There are known risk factors for leukemia, CNS tumors, and breast cancer that must be considered in evaluating the relationship between residential MF and these cancers. Among them, age, sex, year of diagnosis, and socioeconomic status (SES) were controlled for in all seven studies. Of studies which investigated the risk of leukemia, the study of Severson et al. [11] was the only one that took into account the major known leukemogens such as benzene, ionizing radiation and chemotherapeutic agents. None of the four studies of CNS tumors [10, 14-16] evaluated the potential confounding role of vinyl chloride, ionizing radiation, and formaldehyde, which were epidemiologically considered as risk factors for brain tumors [22]. Three studies which assessed the risk of breast cancer [10, 15, 16] did not examine the potential confounding effect of reproductive factors, diet, and radiation [22]. Nevertheless, it can not be concluded that an incomplete adjustment for the above risk factors has been a significant source of bias, since a factor must be associated with both diseases and exposure to produce confounding. There is no clear indication that people living in elevated MF environment may have a greater chance of being exposed to the known carcinogens for such cancers. Moreover, cancer hazards from occupational environments were unlikely to produce substantial confounding effects on the observed risk estimates as well. As a matter of fact, two studies have indicated no evidence of disparity with respect to demographic characteristics and SES indices between people with and without elevated residential MF [23, 24]. Therefore, confounding by known variables is unlikely to explain the observed association between residential MF and adult cancers. However, the likelihood that the observed association was attributable to the confounding by an unknown factor should be kept in mind in further studies, which is particularly important when confronted with a low relative risk estimate in a range between 1.5 and 2.0.

## APPLYING CRITERIA FOR CAUSAL INFERENCE

### Consistency of association

With respect to leukemia, there are no consistent findings. Only three [12-14] out of seven studies have reported an elevated risk. Of them, two reported an elevated risk of myeloid leukemia [13, 14]. The elevated risk of overall leukemia was found in the study of Coleman et al. [12] but not in Feychting and Ahlbom [14]. Among four studies [10, 14-16] that examined the risk of CNS tumors, a positive association was only observed in the analysis of Wertheimer and Leeper [10]. Their study was also the only one suggesting a positive association between MF and breast cancer among three studies of its kind [10, 15-16]. It is noted that the studies with positive results were all based on the case-control design. The two cohort studies [15, 16] showed no evidence to support any positive associations. Although the overall evidence tends to show an inconsistent risk estimate of leukemia and no risk of CNS tumors and breast cancer, it must be noted that this tendency was based on few publications.

### Strength of association and dose-response relation

The epidemiological data showed that the relative risk estimates of leukemia for exposed adult residents were between 1.5 and 3. The corresponding number for CNS tumors was approximately 2.0. Although there are no well-accepted criteria for the strength of association to determine a causal relationship, the relative risk estimate in a range of 1.5 to 3 is considered low and confounding by some unrecognized variables could potentially explain the observed association. However, this does not rule out a causal relationship with a very small relative risk estimate. The only study that showed a dose-response relationship was Wertheimer and Leeper for all cancers in association with MF estimated from wire configurations [10].

Biological coherence and plausibility

There are several hypotheses suggesting the plausibility of a causal relation between MF and cancer. Among them, two biological effects of MF have been identified and replicated in the laboratory: (1) extremely-low-frequency (ELF) electromagnetic impact on pineal gland production of the hormone melatonin in whole animals; and (2) calcium homeostasis in cellular systems. A substantial amount of experimental data indicated that the effect of ELF-MF on cellular biochemistry, function, and structure can be related to the induced current-intensity. However, a majority of the reported effects occurred at current-density levels very much higher than the levels normally found in occupational or residential settings [25]. From this perspective, it is still difficult to identify an underlying mechanism that could support any association between MF and adult cancers.

## CONCLUSIONS

Based on the existing epidemiological results, the putative causal relationship between residential MF exposure and cancers among adults can not be substantiated at this time mainly because of the methodological limitations. Our review reveals that inadequate statistical power is far more a concern than bias. Only two studies [12, 13] had adequate power (0.8) to detect a two-fold risk increase of leukemia, and most of the studies showing no support for the elevated leukemia risk suffered from an inadequate number of study subjects. Bias, on the other hand, is not likely responsible for the positive findings, since no obvious indication of selection bias, information bias, and confounding can be identified. However, measurements of MF were apparently inadequate in most residential adult studies, which may have a source of exposure misclassification.

Residential studies do suggest associations between surrogates of household MF such as wiring configuration and estimated MF and the risks of childhood cancers, primarily leukemia and to a lesser extent brain tumors. The association between childhood cancers and short-term actual measurements of MF, however, is relatively weak. Based on our review, adult leukemia, but not brain tumors, were also suggested to be associated with the surrogate for MF in some residential studies. Unlike residential studies of children, residential adult studies generally lacked actual measurements of residential MF.

As compared to the residential studies as a whole, the occupational studies which investigated the potential carcinogenic effect of MF from workplaces have been numerous and have contributed to a notable epidemiological evidence. Generally, the occupational studies tend to suggest an association between MF from the work environment and leukemia and, to a lesser extent, brain tumors. The occupational studies of breast cancer, so far less comprehensive than those of leukemia and brain tumors, tend to show an inconsistent link between MF and breast cancer risks in male workers. Very few studies which investigated the possible link between female breast cancer and MF from either occupational or home environment have been published.

It is reasonable to conclude that the results and evidence from residential adult studies are less consistent than those from the studies of children and workers. According to a recent review [26], a growing body of childhood and occupational studies indicate that exposure to MF is associated with leukemia, and to a lesser extent with brain tumors. On the other hand, our review reveals no consistent associations of residential MF with leukemia and tends to show no association with brain tumors and breast cancer. Although residential adult studies as a whole did not duplicate the similar tendency observed from childhood and occupational studies, it must be noted that our review is based on a limited number of publications. At present, it is certainly inappropriate to conclude the existence or absence of the carcinogenic effects from residential MF on the basis of essentially inconsistent results from the few residential adult studies published.

With respect to the cell-specific risk of leukemia, one earlier review [27] indicated that occupational studies tended to show a stronger association for AML. This tendency, however, has not been consistently supported by recent occupational studies. Our review reaches no conclusion on the cell-specific risk of leukemia among adult residents because there are insufficient data to separate out the effects of MF on myeloid versus lymphoid leukemia. The cell-specific risks of brain tumors and breast cancer have not been explored extensively by either occupational or residential studies. Most of the studies which examined the cell-specific risk suffered from an inadequate number of study subjects.

Dose-response relationship is another important but not essential criterion for determining causal inferences. Neither childhood nor occupational studies has shown a consistent evidence of dose-response relationships between MF and leukemia or brain tumors. One major weakness of the studies which attempted to evaluate this relationship was the shortage of study subjects, which led to a very unstable relative risk estimate for each exposure category. It can be concluded that the existing evidence from both residential and occupational studies is still unable to clarify whether there is an increasing trend in cancer risk with an increase in MF exposure. Nor is the evidence able to identify certain cell-specific cancers, if any, most sensitive to the MF. These uncertainties will remain with little hope for resolution unless additional epidemiological studies with large number of subjects can be carried out in the future.

The relative risk estimates for leukemia and brain tumors obtained from the four most cited childhood studies [1, 28-30] ranged from 1.5 to 2.5. A meta-analysis of 31 occupational studies of leukemia and 19 studies of brain tumors reported a significantly elevated risk estimate of less than 1.5 for both leukemia and brain tumors [26]. The magnitude of these relative risk estimates is compatible with the strength of association reported from residential adult studies. Because the relative risk estimate is low, any possibility that unknown confounders may have played a role in previous studies should be carefully scrutinized in future studies.

The unknown etiologic role of MF has limited the causal inference of these epidemiological observations. Although there is still no answer at present as to the mechanism by which MF interact with the biological system and therefore cause cancers, it is, however, generally agreed that MF are unlikely to play an essential role in cancer initiation, since no convincing laboratory evidence has been able to indicate that MF cause damage to DNA [31-33]. Rather than playing the role of cancer initiator, the MF might be involved in the carcinogenesis process by enhancing the growth of initiated cells into clone, escaping from eradication by the immune system, or growing tumor mass [25]. To what extent MF are involved in the stages of cancer promotion is unclear. Numerous *in vitro* studies with diverse animal tissues and cultured cells, and *in vivo* studies by animal physiology, behavior, reproduction, growth and development were done in the past, and suggested that changes in biological systems induced by MF exposure may be observed at the molecular, cell, organ, and even the whole organism [25]. Some of these changes may be relevant to the pathogenesis process of cancer. The laboratory studies involving lifetime MF to animals are very limited, giving little data to support or refute the epidemiological findings that MF are able to cause leukemia or brain tumor. It can be concluded that more laboratory studies should be carried out to explain why the associations mainly observed from the epidemiological study are plausible and help resolve controversy as to the potential carcinogenic role of MF.

The direct comparison of the results from residential adult studies with those from childhood studies might not be appropriate, since the etiologic role of MF for adults could be different from that for children. It is of interest, on the other hand, to compare the results from occupational studies with those from residential adult studies. Transmission and substation systems are considered two major external sources of residential MF, which are subject to daily and seasonal variations and, for most "exposed" residences, rarely higher than several mG. On the other hand, MF exposure in workplaces generally does not show the similar variations and is frequently intermittent. In addition, the MF levels in workplaces are generally on the order of 1 to 100 mG, and sometimes even much higher. For example, MF measured near furnaces in the electrosteel industry can reach 80 gausses , and 17 gausses near a spot welding machine [34], which are much higher than the possible peaks in the home environment. Although the MF from residential or occupational sources have dissimilar characteristics, there is no biological belief at this time that these differences have an impact on the risk of adult cancers. Nevertheless, conducting additional residential adult studies with careful avoidance of methodological flaws and with careful control of occupational MF exposure appears to be the direct way to substantiate the above argument and to assess whether MF in the home environment are capable of promoting adult cancers.

In spite that female breast cancer is the leading female cancer in developed countries and a cancer that is increasing rapidly in many parts of the developing world, it's association with MF has not been investigated adequately, especially by the residential studies. Given the prevalence of leukemia and brain tumors in children as well as breast cancer in women, it is suggested that an environmental agent with potential significant public health implications like MF should be considered a potential hazard which needs to be further investigated. Although there is no strong rationale to undertake extensive action immediately to reduce MF in the occupational and home environments, it would be unwise to conclude at present that power frequency MF are not harmful. A practice of "prudent avoidance" of prolonged exposure to MF is warranted and should be exercised during the period of debate and uncertainty.

The controversial question. " *Does MF have anything to do with cancer?* " represents an intriguing scientific problem. It is apparent that there will be no definite answer to the above question until more studies are carried out. Our review reveals a significant shortcoming of residential adult studies at present and suggests that additional residential adult studies with careful avoidance of methodological flaws should be seriously considered. Considering the overall evidence concerning the role of residential MF in the causation of adult cancers, our review also suggests the following aspects to be considered in future residential adult studies. First, the risk of female breast cancer should be further investigated, not only because it is prevalent and has potential for a significant public health implication, but also because women with electrical occupations were not common, and MF exposure at home is considered a major source of MF for most women. Second, future studies should be devoted to the examination of cell-specific types of leukemia and brain tumors, as well as the potential dose-response relationship between residential MF and adult cancers. Third, future studies should attempt to include information on MF exposure from the workplaces in addition to residential exposure in order to estimate the overall MF exposure and evaluate its effect.

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List of Tables and Figures

Table 1. Summary of methodology of epidemiological studies of residential exposure to power frequency MF and adult cancers.

| Author(s) and study period | Study subjects | Exposure assessment |
|---|---|---|
| | *Case-control studies* | |
| Wertheimer et al. (1982)<br>Colorado<br>1967-1975 and 1977 | Deceased or alive cancer, ≧ 19 years of age, selected from cancer death certificates or cancer registry; controls were non-cancer deaths or assembled from neighbors of cases<br>case:control=1179:1179 | Wiring configuration |
| Severson et al. (1988)<br>western Washington State<br>1981-1984 | Incident acute nonlymphoid leukemia aged 20-79 and selected from cancer registry; controls were selected from random digit dialing.<br>case:control=114:133 | 1. Wire configuration<br>2. One-time-only MF measurement<br>3. Exposure classification based on previous 24-hour MF measurement |
| Coleman et al. (1989)<br>south-east England<br>1965-1980 | Cases were leukemia of all ages (n=771) selected from cancer registry; two control groups were used. "cancer controls" registered with a solid tumor excluding lymphoma (n=1432); "population controls" selected from electoral roll (n=231) | 1. Distance between the residence and over-head power lines or substation<br>2. Calculated MF strength from averaged "peak winter load" over three consecutive winters |
| Youngson et al. (1991)<br>North West and Yorkshire regions of | All cases aged 15 or more and registered with non-Hodgkin's lymphoma or myeloid leukemia; controls selected from hospital discharges with non-malignant disease. | 1. Distance from over-head power lines<br>2. Calculated MF from maximum current load in the 5 years preceding the |

| | | |
|---|---|---|
| England<br>1983-1985 | case:control=2113:2113 (lymphoid malignancy); 801:801 (myeloid leukemia) | key date |
| Feychting and Ahlbom (1994)<br>Sweden<br>1960-1985 | Cases and controls were selected from a cohort of some 400,000 people living within 300 m of 220/400 kV power lines. All subjects aged >15.<br>325 leukemia; 223 central nervous system tumors; 1091 controls | 1. Spot measurement of MF<br>2. Calculated MF strength from over-head power lines.<br>3. Distance from over-head power lines |
| | *Cohort studies* | |
| McDowall (1986)<br>East Anglia, UK<br>1971-1983 | Retro-cohort of 7,631 residents of all ages and living within 50 m radius of a substation or within 30 m either side of an over-head power line in the 1971 Census. Expected deaths were calculated from regional general population<br>Person years at risk=91,016 | In the vicinity of electricity transmission system |
| Schreiber et al. (1993)<br>Limmel, The Netherlands<br>1961-1981 | Retro-cohort of 3,549 residents of all ages who have lived in Limmel, The Netherlands for 5 years or more between 1961-1981. Expected deaths were calculated from Dutch general population.<br>Person years at risk=74,055 | In the vicinity of 2 over-head power lines and 1 transformer substation. |

Table 2. Summary of findings of studies of residential exposure to EMF and adult cancers*

| Study | Main findings | |
|---|---|---|
| Wertheimer and Leeper (1982) | All cancer *C-ratio*† 1.39 ($p$<0.0001); Significant high *C-ratios* were observed for cancer of nervous system, uterus, breast, and lymphomas. The result for leukemia was null. | |
| | | All cancers |
| | Very low | OR=1.00 |
| | Ordinary low | OR=1.46 (1.11-1.93)‡ |
| | Ordinary high | OR=1.66 (1.20-2.24) |
| | Very high | OR=2.18 (1.48-3.22) |
| Severson et al.(1988) | *Wiring configuration, longest residence 3-10 years before reference date* | |
| | | Acute nonlymphoid leukemia |
| | Very low | OR=1.00 |
| | Ordinary low | OR=0.60 (0.29-1.22) |
| | Ordinary high | OR=0.77 (0.35-1.68) |
| | Very high | OR=0.79 (0.22-2.89) |
| | *Wiring configuration, residence closest to reference date* | |
| | Very low | OR=1.00 |
| | Ordinary low | OR=0.81 (0.41-1.61) |
| | Ordinary high | OR=1.36 (0.62-2.96) |
| | Very high | OR=0.84 (0.24-2.93) |
| | *Unweighted mean exposure (mG) based on spot measurements, residence closest to reference date (low power configuration)* | |
| | 0-0.5 | OR=1.00 |
| | 0.51-1.99 | OR=1.16 (0.52-2.56) |
| | ≧ 2.00 | OR=1.50 (0.48-4.69) |
| | *Time-weighted mean exposure (mG) based on spot measurements, residence closest to reference date (low power configuration)* | |
| | 0-0.5 | OR=1.00 |
| | 0.51-1.99 | OR=1.17 (0.54-2.54) |
| | ≧ 2.00 | OR=1.03 (0.33-3.20) |

| | | | | |
|---|---|---|---|---|
| | *Exposure classification (mG) based on previous 24-h measurements, longest residence 3-10 years before reference date* | | | |
| | 0-0.5 | OR=1.00 | | |
| | 0.51-1.99 | OR=0.69 (0.37-1.32) | | |
| | ≧ 2.00 | OR=0.75 (0.31-1.80) | | |
| | *Exposure classification (mG) based on previous 24-h measurements, residence closest to reference date* | | | |
| | 0-0.5 | OR=1.00 | | |
| | 0.51-1.99 | OR=0.80 (0.47-1.36) | | |
| | ≧ 2.00 | OR=0.97 (0.47-1.98) | | |
| Coleman et al. | *Distance (m) from over-head power lines* | | | |
| | | <u>All leukemia</u> | | |
| (1989) | >99 | OR=1.00 | | |
| | 50-99 | OR=1.33 (0.37-4.73) | | |
| | 25-49 | OR=2.00 (0.28-14.23) | | |
| | 0-24 | OR=2.00 (0.12-32.02) | | |
| | *Distance (m) from nearest substation* | | | |
| | >99 | OR=1.00 | | |
| | 50-99 | OR=0.99 (0.81-1.20) | | |
| | 25-49 | OR=0.89 (0.64-1.23) | | |
| | 0-24 | OR=1.26 (0.81-1.97) | | |
| Youngson et al. | *Distance from over-head power lines* | | | |
| (1991) | | <u>Myeloid leukemia</u> | <u>Lymphoid malignancies</u> | |
| | >99 | OR=1.00 | OR=1.00 | |
| | 50-99 | OR=1.39 (0.82-2.53) | OR=0.82 (0.60-1.17) | |
| | 25-49 | OR=1.02 (0.53-1.96) | OR=1.18 (0.70-1.98) | |
| | 0-24 | OR=1.47 (0.74-2.92) | OR=1.10 (0.72-1.69) | |
| | *MF (mG) estimated from maximum current load* | | | |
| | | <u>Myeloid leukemia</u> | <u>Lymphoid malignancies</u> | |
| | <0.1 | OR=1.00 | OR=1.00 | |
| | 0.1-0.9 | OR=1.06 (0.66-1.72) | OR=0.92 (0.64-1.33) | |
| | ≧ 1.0 | OR=3.00 (0.81-11.08) | OR=0.90 (0.47-1.71) | |
| Feychting and Ahlbom (1994) | *MF (mG) calculated from load on the lines, residence closest to reference date* | | | |
| | | <u>AML</u> | <u>CML</u> | <u>CNS tumors</u> |
| | <1 | OR=1.0 | OR=1.0 | OR=1.0 |
| | 1-1.9 | OR=1.0 (0.4-2.5) | OR=1.4 (0.5-3.3) | OR=1.1 (0.7-2.0) |
| | ≧ 2 | OR=1.7 (0.8-3.5) | OR=1.7 (0.7-3.8) | OR=0.7 (0.4-1.3) |

| | | | | | |
|---|---|---|---|---|---|
| | *Cumulative MF (mG-years) calculated from load on the lines, 15 years preceding reference date* | | | | |
| | | AML | CML | CNS tumors | |
| | <1 | OR=1.0 | OR=1.0 | OR=1.0 | |
| | 1-1.9 | OR=1.5 (0.5-3.7) | OR=0.7 (0.1-2.6) | OR=1.1 (0.6-2.1) | |
| | ≧ 2 | OR=2.3 (1.0-4.6) | OR=2.1 (0.9-4.7) | OR=0.7 (0.3-1.3) | |
| | ≧ 3 | OR=1.9 (0.6-4.7) | OR=2.7 (1.0-6.4) | OR=0.7 (0.3-1.5) | |
| | *MF (mG) from spot measurements* | | | | |
| | | AML | CML | CNS tumors | |
| | <1 | OR=1.00 | OR=1.00 | OR=1.0 | |
| | 1-1.9 | OR=0.9 (0.3-2.3) | OR=0.6 (0.2-1.8) | OR=1.2 (0.7-2.0) | |
| | ≧ 2 | OR=1.1 (0.4-2.4) | OR=1.5 (0.7-3.2) | OR=0.8 (0.5-1.3) | |
| | *Distance(m) from power lines* | | | | |
| | | AML | CML | CNS tumors | |
| | ≧ 101 | OR=1.0 | OR=1.0 | OR=1.0 | |
| | 51-100 | OR=1.3 (0.7-2.5) | OR=1.0 (0.4-2.1) | OR=1.1 (0.7-1.7) | |
| | ≦ 50 | OR=1.1 (0.4-2.8) | OR=2.4 (1.0-5.1) | OR=1.0 (0.6-1.8) | |
| McDowall (1986) | *Distance (m) from electrical installations* | | | | |
| | | All cancers | Leukemia | Breast cancer | |
| | 35-50 | SMR=95 (76-117) | SMR=120 (25-351) | SMR=37 (1-206) | |
| | 15-34 | SMR=105 (85-128) | SMR=77 (9-278) | SMR=122 (61-219) | |
| | 0-14 | SMR=103 (68-150) | SMR=143 (4-796) | SMR=110 (53-202) | |
| Schreiber et al. (1993) | *Distance (m) from power lines* | | | | |
| | | All cancers | Leukemia | Brain tumors | Breast cancer |
| | >100 | SMR=85 (63-114) | SMR= — | SMR=— | SMR=96 (31-223) |
| | ≦ 100 | SMR=93 (72-118) | SMR=132 (27-386) | SMR=196 (40-574) | SMR=128 (58-243) |

* When relative risk estimates and confidence intervals are not presented in the papers, they were calculated from available data. Some relative risk estimates were calculated from re-categorized exposures for the purpose of comparisons.

† $C\text{-}ratio = \dfrac{\text{Number of matched pairs in which the case shows a higher current configuration}}{\text{Number of matched pairs in which the control shows a higher current configuration}}$

‡ 95% confidence interval.

§ Abbreviation: OR: odds ratio; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; CNS: central nervous system; SMR: standardized mortality ratio; m: meter; mG: milligauss.

Table 3. Statistical power of studies to detect relative risk of adult cancers for people with elevated exposure to residential MF.

| Study | Main contrasts | Type of cancer | Power* |
|---|---|---|---|
| Wertheimer and Leeper | VHCC vs VLCC | All cancers | 0.72 |
| Severson et al. | VHCC vs VLCC | Acute nonlymphoid leukemia | 0.45 |
| | ≧2 mG vs ≦0.5 mG | Acute nonlymphoid leukemia | 0.57 |
| Coleman et al. | 0-24 m vs ≧100 m from power lines | All leukemia | 0.43 |
| | 0-24 m vs ≧100 m from substations | All leukemia | 0.94 |
| Youngson et al. | 0-24 m vs ≧100 m from transmission lines | Myeloid leukemia | 0.99 |
| | 0-24 m vs ≧100 m from transmission lines | Lymphoid malignancies | 0.95 |
| | ≧1 mG vs <0.1 mG | Myeloid leukemia | 0.16 |
| | ≧1 mG vs <0.1 mG | Lymphoid malignancies | 0.75 |
| Feychting and Ahlbom | ≧2 mG vs <0.1 mG from calculation | Acute myeloid leukemia | 0.48 |
| | ≧2 mG vs <0.1 mG from calculation | Chronic myeloid leukemia | 0.41 |
| | ≧2 mG vs <0.1 mG from calculation | Central nervous system tumors | 0.94 |
| | ≧2 mG vs <0.1 mG from spot measurements | Acute myeloid leukemia | 0.46 |

| | | | |
|---|---|---|---|
| | $\geqq$2 mG vs <0.1 mG from spot measurements | Chronic myeloid leukemia | 0.46 |
| | $\geqq$2 mG vs <0.1 mG from spot measurements | Central nervous system tumors | 0.88 |
| McDowall | exposed population vs general population | Leukemia | 0.17 |
| | exposed population vs general population | Breast cancer | 0.97 |
| Schreiber et al. | exposed population vs general population | Leukemia | 0.17 |
| | exposed population vs general population | Brain tumors | 0.17 |
| | exposed population vs general population | Breast cancer | 0.59 |

* Power to reject a null effect at the 0.05 significance level if in fact the true relative risk estimate is two.

Title of Manuscript II

Long-term Residential Exposure to 60 Hz Magnetic Fields and Risks of Adult Cancers in Taiwan

## ABSTRACT

A case-control study, using matching on date of birth, sex, and date of diagnosis, was carried out in northern Taiwan to evaluate the risk of adult ($\geqq$ 15 years of age) leukemia, brain tumors, and female breast cancers in relation to residential exposure to 60 Hz magnetic fields (MF). Cases were newly diagnosed cancers reported to the cancer registry between 1987 and 1992 and controls were incident cancers from sites other than those previously suspected of being associated with MF during the same period. Assessment of MF in the residence occupied by the study subjects at time of diagnosis was performed by modeling power information of high-voltage transmission lines. This surrogate method was validated by actual measurements in a sample of residences. The results were based on the separate analysis of 708 leukemia, 455 brain tumors, and 1,562 female breast cancers. The risk of leukemia for exposure to MF > 0.2 μT relative to the reference level (< 0.1 μT) was significantly elevated (odds ratio (OR)=1.51, 95% confidence interval (CI) 1.05-2.19). A dose-response relationship showed a gradient increase of relative risk estimates for leukemia with MF. The relative risk estimates for brain tumors and female breast cancers were slightly elevated, but were statistically compatible to null. The above results remained unchanged after adjusting for sex, age and date at diagnosis, urbanization, and neighboring industrial parks. Additional information revealed that social class, reproductive variables and other characteristics of study subjects with and without elevated residential MF were quite similar and appeared to have no influence on the observed results. Our data support the association of residential MF with the risk of leukemia, but not with the risks of brain tumors and female breast cancer in adults.

Key words: magnetic fields; leukemia; brain tumors; breast cancer; risk factors

Over the past decades, there has been increasing concern about the possible carcinogenic effect of residential and occupational exposure to power frequency (50 or 60 Hertz (Hz)) magnetic fields (MF). This concern began with the epidemiological study of Wertheimer and Leeper in 1979 (1) reporting an association between wire codes near the house and childhood cancer. Power frequency electric and magnetic fields are everywhere and noticeably elevated in proximity to power generation, transmission, and distribution facilities, and other electrical equipment and appliances. Because MF, unlike electric fields, are hardly influenced or shielded by electrically conductive materials and penetrate buildings, trees, and organisms (2), most studies put emphasis upon its potential biological effect. Recent occupational studies have included extensive MF exposure assessments (3-6) and have provided methodologically sound epidemiological evidence linking occupational exposure to MF and certain types of cancer. Among residential studies of childhood cancer, the most notable studies are four case-control studies (1, 7-9). All of them reported an association between residential MF and childhood cancer, especially leukemia. Studies of adult cancer in relation to residential MF exposure have been neither as extensive nor as consistent as the childhood and occupational cancer studies in reporting an association between MF and increased cancer risks. To our knowledge, there were seven residential studies so far investigating the link between adult cancer and household MF (10-16). Interpretation of the association observed from residential adult studies was hampered mainly due to methodological limitations. The present study was carried out to estimate the risks of leukemia, brain tumors, and female breast cancers in adults with elevated residential exposure to 60 Hz MF.

## MATERIALS AND METHODS

### Background

The present study, using the case-control design, was conducted to examine the potential risks of leukemia, brain tumors, and female breast cancers posed by long-term residential exposure to 60 Hz MF among adults aged 15 and more. The study area encompassed four administrative districts of northern Taiwan. They were Taipei city, Taipei county, Keelung city and Taoyuan county. The study period for leukemia and brain tumors was between 1987 and 1992, whereas for female breast cancers it was between 1990 and 1992. The size of the population aged 15 or more in the study area was 2,589,678 males and 2,455,512 females in 1987. The corresponding numbers for 1992 were 2,863,649 and 2,772,243, respectively (17). Between 1987 and 1992, there were 64,599 adult cancers (all types) diagnosed and reported to the Cancer Registry of Department of Health (DOH), Taiwan. Among them, 1,135 were leukemia, 705 were primary brain tumors, and 2,407 were female breast cancers (1990-1992 only). The power lines with voltage equal or higher than 69 kilo-volts (kV) were considered the main sources of indoor 60 Hz MF in the study area. Five types of transmission lines (69 kV with one circuit (n=34), 69 kV with two circuits (n=63), 161 kV with one circuit (n=3), 161 kV with two circuits (n=20), and 345 kV with two circuits (n=1)) were in service in the study area between 1987 and 1992, which gave rise to a total of 1,474 circuit-kilo-meters (CKMs) (18). Taking into account the 3,968 $km^2$ area within the study boundary, the density of high-voltage power lines was estimated to be 0.3715 CKM per $km^2$.

Study subjects

The cancer registry. All eligible study subjects were identified from the Cancer Registry. The cancer reporting system has been operating since 1979. Pathologically confirmed incident cancer patients are reported from 265 hospitals including all medical centers and teaching hospitals nationwide on a regular basis. Registry information includes name, personal identification number, date of birth, date of diagnosis, gender, address at diagnosis, hospital in which the cancer was diagnosed, and *International Classification of Diseases for Oncology* (ICD-O) including Topography-code and Morphology-code. The quality of the Cancer Registry has been described in detail elsewhere (19). In summary, the inaccuracy rate of gender, age at diagnosis, topography-code, and address at diagnosis was 0.6 percent, 3.7 percent, 4.1 percent, and 10.2 percent. The figures were derived from comparing medical files of 1,058 pathologically confirmed cancer patients newly diagnosed from 45 randomly selected hospitals islandwide between 1984 and 1986 with the Cancer Registry data. The quality-analysis study (19) did show moderate, but not statistically significant, geographic variation in the rate of accuracy. Within the study boundary of the present study, the inaccuracy rates for sex, age at diagnosis, and topography-code were lower than average by some 5 percent, but that for addresses at diagnosis was slightly higher than the average. As for the completeness of coverage of incident cancer cases, the quality-analysis study showed that more than 85 percent of liver and pancreatic cancer deaths in 1991, selected from the national mortality records and presumed to be covered by the Cancer Registry somewhere between 1979 and 1991 because of their unfavorable survivals, were successfully traced back to the Cancer Registry. The incomplete coverage suggested an underreporting by some hospitals rather than an incomplete coverage of hospitals, since all the island's major hospitals reported cases to the registry. Again, no substantial geographic variation in completeness of coverage was observed.

In order to ascertain whether both accuracy and completeness of the registry have improved in recent years, we conducted a preliminary analysis in which 231 randomly selected incident cancer cases diagnosed at National Taiwan University Hospital (NTUH) in the year of 1991 or 1992, representing about 9.9% of all cancer patients diagnosed during the two-year period at NTUH, were compared with the registry. Of the 230 subjects who were successfully traced, the address at diagnosis for 6 (2.6 percent) cases and the topography code for 5 (2.0 percent) cases were found to be inconsistent with the registry. Additionally, the completeness of coverage seemed improving since nearly all cases were successfully traced to the registry. We can not exclude the possibility that the results from our preliminary analysis were selective, considering the use of data from only one medical center. However, it appears that the quality of the registry data is now very reliable. In addition to computerization errors, missing information on variables, especially address at diagnosis, was not uncommon in early years. This situation improved after 1985 and the information for each individual record has been almost complete since then.

Based on the quality of registry data, the required sample size, and the available number of cases and the pre-determined sample size, it was decided to use all cancer cases registered between 1987 and 1992 (n=64,599) from which cases and corresponding controls for the present study were selected. Exclusion of the recent two years, 1993 and 1994, was due to the fact that data computerization and correction for reports submitted from hospitals have not yet been completed.

Cases and controls. Among 64,599 adult cancer patients ($\geqq$ 15 years of age) residing in northern Taiwan at diagnosis between 1987 and 1992, 1,135 were leukemia (ICD-O: 980-994), 705 were brain tumors (ICD-O: 191), and 2,407 were female breast cancers (ICD-O:174) (between 1990 and 1992 only). Incident cancers were used to form the case series. The potential controls (n=42,968) were the other cancer patients with a diagnosis other than cancers of the hematopoietic and reticuloendothelial systems (ICD-O: 169), male breast (ICD-O: 175), skin (ICD-O: 173), ovary, fallopian tube, and broad ligament (ICD-O: 183), and prostate gland (ICD-O: 185) . Exclusion of above cancer categories from the control candidates was done to avoid the selection bias resulting from having among control cancers those have had a link with MF (20). Because cancers of hematopoietic and reticuloendothelial system other than leukemia may share with leukemia the same risk factors and male breast cancer has been suspected of being associated with MF in previous epidemiological studies (21-23), these two cancer types were excluded from the control candidates. The other cancers eliminated from the potential controls were hormone-related cancers (24) which could be associated with MF if the suppression of melatonin eventually turned out to be the true underlying interaction mechanism between MF and human body (25). For each case, one control was randomly selected by matching on age at diagnosis ($\pm$ 5 years), sex, and date of diagnosis ($\pm$ 6 months). Controls for all cases were successfully identified.

Examination of information for study subjects. After the selection process was completed, we further examined the 4,247 pairs of study subjects (1135 pairs for leukemia, 705 pairs for brain tumors, and 2407 pairs for female breast cancers) on cancer diagnosis and address at diagnosis. The registry data were verified by the information shown on the formatted reports submitted from hospitals. The registry was also checked for possible duplicate registrations. The selected control was replaced with another one when one of the following errors was noticed: missing information on address at diagnosis; pathological confirmation not noted by the Cancer Registry; and being selected more than once due to duplicate registrations. Among cases, 42 of them (11 leukemia, 9 brain tumors, and 22 female breast cancers) were found to have at least one of the preceding three errors and were then excluded along with their corresponding controls. This exclusion reduced the number of pairs for leukemia, brain tumor, and female breast cancers to 1124, 696, and 2385, respectively.

Assessment of residential MF exposure

Residential and power line route maps and utilities information. Large-scale maps showing individual street and residential locations were provided by 31 authorities of local administrative districts which correspond to 69 percent of all local administrative districts (n=45) in the study area. The maps were not identical with scales ranging from 1 in 5,300 (1.89 mm=10 m) to 1 in 10,000 (1.00 mm=10 m). The unavailability of maps for the remaining 14 districts meant that exposure assessment for subjects residing in those areas would not be available. The case/control left eventually for exposure assessment was 870/889, 577/552, and 1980/1880, for the group of leukemia, brain tumors, and female breast cancers, respectively. Among them, the number of pairs still preserved was 708, 455, and 1562. The analysis linking exposure indices to the risk of cancers was restricted to those pairs.

According to the document and utility maps provided by the Department of Transmission and Substation Project (DTSP), a technical institute affiliated with Taiwan Power

Company (TPC), there are currently 124 high-voltage (69/161/345 kV) transmission lines in service within the study boundary. Three of them installed after 1992 were excluded. Among the remaining 121 power lines, the dates of installation were between 1957 and 1992. Additionally, no power lines that were in service during the study period (1987-1992) were removed after 1992. Thus, these 121 transmission lines were considered the main source of residential MF exposure during the study period and their potential of emitting MF were assessed. The power information including wire configurations, annual average and maximum loads on the lines for years between January 1984 and August 1994, the current phase, maximum net current through earth as a percentage of average phase current, and geographical resistivity of earth were also supplied by the DTSP. We also referred to the maps of neighboring administrative districts of the study area and confirmed that no power lines outside the study boundary were within 200 meters of the edge of study area, indicating that MF of residences occupied by study subjects were unlikely to be affected substantially by transmission lines outside the boundary of the study area.

Determination of distance between residences and power lines. In addition to the power information, the lateral distance of each residence from transmission lines and the height of each residence above ground are two other elements necessary to calculate residential MF.

The horizontal distance between each residence and middle wire of three-phase transmission lines was determined stepwise. After the study subjects were selected, a unique identification number from 1 to 8410 was randomly assigned to each subject (including 1,662 subjects whose residential MF were undetermined and 1,298 subjects whose pairs were not preserved). The subject's case/control status was kept unknown throughout the entire course of exposure assessment. The residences of 6,748 subjects were then inscribed on the residential maps. After the completion of inscription, these maps were sent to the DTSP in order to generate, using the DTSP's pre-computerized utility maps, utility route maps with scales completely identical to these residential maps. By overlapping utility route and residential maps, it was possible to measure the horizontal distance between each residence and transmission lines nearest it. Due to the limitation of scaled residential maps, the flat distance of each residence to transmission lines was determined with a unit of 10 meters. The residential MF was assessed at a location one meter above ground. For apartments, the height between floors within a building was arbitrarily assumed to be three meters.

Modeling indoor MF. The transmission lines in the study area were three-phase lines with current differences by a phase angle of 120 degree. The three phase conductors were vertically configured. The residential MF were calculated by using a PC software created by RG Olsen from Washington State University under contract to the Bonneville Power Administration. The development of this software is described elsewhere (26).

With wire configurations, lateral distance from transmission lines and residential height above ground, residential MF for the year of diagnosis was then calculated for each study subject. Based on annual maximum and average current, two exposure indices, maximum and average residential MF, were calculated for each study subject. The estimated MF was categorized into three levels with cutoff points of 0.1 micro-Tesla ($\mu$T) and 0.2 $\mu$T in which exposure > 0.2 $\mu$T was considered elevated exposure and exposure less than 0.1 $\mu$T was used as the reference group.

Validation of estimated MF

In order to evaluate the accuracy of estimated MF, 407 residences occupied by a sample of study subjects were selected for validation (*the selection process has been described in detail in METHODS of manuscript III*) . The selected residences were measured by the EMDEX Electric and Magnetic Field Digital Exposure System (27), a hardware and software package designed to measured, record, and analyze power frequency electric and magnetic fields. The EMDEX II is a programmable data-acquisition meter that measures the x, y, z vector components of the MF through its internal sensors. Measurements are stored in the meter's memory and later transferred through a serial communication port to a PC for storage, display and analysis. The measured MF were compared with estimated MF. All actual measurements were performed between November 1994 and May 1995. The measurement protocol and the agreement between measured and estimated MFs are described elsewhere (28). In summary, almost all measurements were performed at a low-power condition (household power was turned off). The indoor measurement was conducted over approximately 30-40 minutes with sampling time interval of 30 seconds giving rise to roughly 70-80 readings in average for each residence. The intra-class correlation coefficient (ICC) between measured and estimated MFs was very high (ICC=0.9). When categorized into ordinal scale (<0.1 μT, 0.1-0.2 μT, >0.2 μT), the measured and estimated MFs showed an agreement of 0.64 (kappa (K)=0.64, 95 percent CI 0.50-0.78). The agreement between categorized MF increased to 0.72 (95 percent CI 0.62-0.82) when a 0.5 weight was assigned to allow for partial agreement.

Potential confounders

Previous studies have shown an association between urbanization and certain types of cancer in Taiwan (29, 30). We used an index of urbanization which is determined by population density, age composition, mobility, economic activity and family income, educational level, and sanitation facilities (31) to adjust for urbanization. Whether residence near to an industrial park was used as a surrogate for occupational and environmental hazards on the grounds that subjects living in a district with an industrial park were considered to have more chance of exposure to occupational or environmental hazards produced by centralized factories.

Because it is a condition of access to the Cancer Registry that no interview with study subjects was allowed, the other risk factors for cancers could not be obtained directly from study subjects. We alternatively retrieved the other potential confounders from the medical centers in which a brief questionnaire has been regularly completed by hospitalized patients or their next of kin (all cancer patients are presumably hospitalized). This questionnaire covered demographic data (age, weight, and height at hospitalization, sex, birth place, marriage status, and religion), educational level, occupational categories, medical history, and smoking. Some reproductive information were also available for gynecological patients which included age at menarche, menopause status, menstrual pattern, number of births, age at first labor, and breast feeding history. Among 6,748 subjects (2,725 pairs and 1,298 subjects without their pairs preserved) with exposure data, 2,401 subjects (1,163 cases and 1,238 controls) were diagnosed at four medical centers in northern Taiwan. Of them, 2,288 (1,115 cases and 1,163 controls) patients have completed the questionnaires during their hospitalization. The association between these cancer risk factors and residential MF was evaluated to provide information concerning the potential of these variables to produce confounding effects.

Statistical Analysis

The risk of leukemia, brain tumor, and female breast cancers was analyzed separately throughout the analysis. Relative risks were estimated for two categories of elevated residential MF (>0.2 μT and 0.1-0.2 μT) relative to the low residential MF environment (<0.1 μT).

The variables used to characterize study subjects included age, height and weight at diagnosis, sex, education level, smoking, medical X-ray exposure, age at menarche, menopause status, self-reported irregular period, number of birth, age at first labor, and breast feeding experience. The age, height, and weight were measured on continuous scale; the rest of variables were divided into categories. The distribution of each variable was presented and compared between study subjects with different residential MFs.

Crude ORs were computed from two by two tables. Multiple conditional logistic regression analysis was used for calculation of the adjusted odds ratio (OR) to estimate the relative risks (32, p.187-213.). Two-sided 95 percent confidence intervals (CI) were calculated by the test-based method (33). Dose-response relationship analysis was carried out by fitting a linear term for MF coded 1, 2, and 3 and treated as a continuous variable in the multivariate model. The covariates adjusted for reduction of potential confounding were categorical age groups, sex, year of diagnosis, urbanization, and whether or not living close to an industrial park. Exploratory analyses included the calculation of sex-specific ORs; age-specific ORs using the median age among three control series, 47, as the cutoff point; and ORs for cell-specific cancers. The ORs for leukemia and brain tumors groups were used to estimate the relative risks between 1987 and 1992; while ORs for female breast cancer estimated the relative risks between 1990 and 1992.

## RESULTS

The study groups and attrition of study subjects are given in Table 1. Approximately 64 percent of the possible pairs were preserved in each cancer category. Also shown in Table 1 are the number of participants who completed a brief interview during hospitalization and the number of participants for whom an indoor MF measurement was conducted. The proportion of participants completing questionnaires or receiving indoor measurement was similar among study groups. Table 2 compares the distributions of age at diagnosis, sex, year of diagnosis, and characteristics of administrative districts in study area (urbanization, living district, and industrial parks) between cases and controls. As expected, all three study groups showed a close matching between cases and controls with respect to matching variables and variables related to the living districts. Because Taipei metropolitan area is included within the boundary of the study area, more than 50 percent participants were living in highly urbanized districts (urbanization I). Approximately a quarter of the study subjects lived in districts where there was at least one industrial park.

The ORs, using both annual average and maximum current of residential MF, for exposure between 0.1 and 0.2 μT and >0.2 μT relative to the reference exposure (< 0.1 μT) are presented in table 3. For leukemia, the crude OR based on estimated MF for exposure >0.2 μT was significantly elevated at 1.51, 95 percent CI 1.05-2.19; for exposure between 0.1 and 0.2 μT, the crude OR was 1.35, 95 percent CI 0.82-2.21. For brain tumors and female breast cancers, the crude ORs for exposure >0.2 μT were slightly elevated but were statistically compatible to null (1.27, 95 percent CI 0.84-1.93 and 1.17, 95 percent CI 0.93-1.48, respectively). The crude ORs for exposure between 0.1 and 0.2 μT in both brain tumors and female breast cancers were close to one. A trend test yielded a $p$ value of 0.013 for leukemia, indicating a dose-response relationship between leukemia and gradient levels of residential MF. The increasing trend, on the other hand, was observed neither in brain tumors nor in female breast cancers. Results from analyses that used estimated maximum MF were very similar to those based on the estimated average MF. Additionally, the relative risk estimates presented in Table 3 were almost unchanged when adjusting for matching variables, urbanization, and neighboring industrial park.

Because our data showed a similar association of cancer with estimated average and maximum MF, we used estimated average MF in the exploratory analyses. Among cell-type specific leukemia, the most elevated risk for exposure > 0.2 μT was observed for acute lymphoid leukemia (ALL) with a crude OR of 2.88, 95 percent CI 0.99-8.76. The crude ORs for the same contrast (i.e.,>0.2 μT Vs <0.1 μT) was 1.11 (95 percent CI 0.03-42.97), 1.27 (95 percent CI 0.72-2.26), and 1.39 (95 percent CI 0.61-3.17) for chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML), respectively. With the exception of glioblastoma whose crude OR was 1.60, 95 percent CI 0.69-3.78, the remaining ORs of other gliomas for exposure > 0.2 μT relative to < 0.1 μT were close to one. The ORs of ductal, lobular, and medullary neoplasm as well as malignant epithelial tumors for elevated exposure were all close to one. The results from all subgroup analyses were not very reliable because of limited sample size which impeded conclusions from these analyses.

Table 4 presents the relative risk estimates by age groups. Although younger adults (age equal or below 47) with exposure >0.2 μT experienced a higher risk of leukemia than older adults, these differences are comparable with chance. Results for brain tumors and female breast cancers groups were somewhat different; older people were at a somewhat higher estimated risk than younger people, although again those differences were comparable with chance.

The crude OR of leukemia for males with exposure >0.2 μT, compared with male subjects with exposure <0.1 μT, was 1.65, 95 percent CI 1.00-.2.73, which was the only statistically significant finding in the exploratory analyses. With the same contrast between exposures, the crude OR of leukemia for females was 1.36, 95 percent CI 0.77-2.39. The crude OR of brain tumors for exposure >0.2 μT relative to <0.1 μT, was 1.19, 95 percent CI 0.70-2.02 for males and 1.44, 95 percent CI 0.72-2.92 for females, respectively. Again, the interaction of MF and sex was not statistically significant at 0.05 significance level for both leukemia and brain tumors (Table 5). The *a posteriori* assessment of interactions of MF exposure and age and sex in the three study groups reached no reliable evidence to draw any conclusion.

Without performing statistical testing, most of the risk factors for leukemia, brain tumors, and female breast cancers listed in Table 6 showed a roughly even distribution among subjects in the three different exposure (<0.1 μT, 0.1-0.2 μT, >0.2 μT) except age at diagnosis. Subjects with exposure >0.2 μT were older than those with other exposure groups at time of cancer diagnosis, suggesting a dissimilar age composition between populations with different exposure levels. However, this phenomena was not duplicated when all 5,450 study subjects were analyzed. Among variables, education, a conventional component of socioeconomic status (SES), was similar in population with and without elevated exposure, suggesting that SES was not associated with residential MF in our data. Additionally, reproductive factors were not found to be related to residential MF as well.

Our analysis suggested that the characteristics of study subjects with different exposure levels were comparable.

DISCUSSION

The results from the present study provided some evidence linking residential exposure to 60 Hz MF to the risk of leukemia in adults aged 15 or more. With the same design and analysis, on the other hand, neither were brain tumors nor female breast cancers found to be significantly associated with elevated residential MF. Analyses of cell-specific leukemia and brain tumors showed that although subjects with elevated MF were at a higher estimated risk of ALL, AML and glioblastoma. these results were based on limited sample size and were compatible with the null statistically.

The increased leukemia risk for an exposure above 0.2 $\mu$T was statistically significant for males but not for females. For brain tumors, a difference in sex-specific risk estimates was also observed in which females were at a higher risk than males. However, the differences in relative risk estimates of leukemia and brain tumors between sexes were not statistically significant to suggest an interaction between residential MF and sex. Moreover, although our data tend to show that younger adults ($\leq$ 47 years of age) were at a higher estimated risk of leukemia, whereas older adults were at a higher estimated risk of brain tumors and female breast cancers, the evidence concerning the interaction between residential MF and age was not statistically significant either. Overall, the exploratory *a posteriori* analysis of sex-specific and age-specific risks reached no consistent findings across study groups, which limits the inference of effect modification by sex and age on the carcinogenic effects of MF. The sample size for estimating sex-specific and age-specific risks was clearly inadequate and responsible for the wide confidence intervals of relative risk estimates. In addition, we did not take into account the multiple-comparison procedures in evaluating the significance of age or sex-specific relative risk estimates, which may compromise the statistically significant OR of leukemia observed among men.

This study has several strengths. First, using cancer registers as source of study subjects, it was a registry-based case-control study in which cases and controls presumably came from the same population. Although the completeness of the Cancer Registry was not perfect, which possibly led to an incomplete coverage of leukemia, brain tumors, and female breast cancers in northern Taiwan during the study period, this incomplete coverage would also have applied to the controls, since the incomplete coverage of cancer was not likely to be selective. Therefore, any selection bias of cases that may have resulted from factors associated with both incomplete coverage and residential MF would also apply to controls. Second, the selection of cancer controls was mainly for "practical" consideration, since they were already at hand and made it easy to perform the pair-matching process. In fact, the use of cancer controls has several advantages. Examination of the specificity of an exposure for a particular type of cancer and "practical" reasons are two of them (34). The only concern here was the potential selection bias due to unknown associations between MF and certain cancers that have not been associated with MF in previous studies. This could have been likely to play in the direction of minimizing a real association. However, the exclusion criteria set for recruiting controls reduced this potential of selection bias. Third, the measurement of historical exposure to MF is a challenge to all retrospective studies, since direct information concerning past MF is always lacking. Because historical power information of high-voltage transmission lines were routinely recorded in Taiwan, we were able to use power information of transmission lines to model past residential MF. The exposure assessment method used in this study was considered superior to those simply assuming that measurements of MF in today's environments are highly correlated with MF of the past. Fourth, residential MF exposure having been assessed blind of disease status, the information bias frequently occurring during exposure assessment due to the knowledge of diseases and underlying hypotheses was avoided.

Although it was reasonable to assume that high-voltage transmission lines are the most essential determinant of indoor MF for residences in their proximity, it was certainly necessary to address how the ignorance of other sources of MF, for example, distribution power lines, may have affected the validity of exposure assessment used in the present study. Our data showed that indoor MF for almost all residences located more than 200 meters from transmission lines were calculated to be less than 0.01 μT, and almost zero for residences with a lateral distance of 250 meters or more from transmission lines. According to a survey conducted in northern Taiwan which showed that the background residential MF were between 0.01 and 0.02 μT (35) and considering the results from actual measurements on a sample of residences occupied by study subjects (28), MF for the residences located more than 200 meters from transmission lines were apparently underestimated. This underestimation resulted from not taking into account the other sources of 60 Hz MF such as distribution lines, power transformer, and appliances in the residences. Therefore, exposure misclassification resulting from measurement errors were expected in this study, which was further empirically suggested by an agreement of 0.64 (Kappa=0.64, 95 percent CI 0.50-0.78) between measured and estimated MFs. However, measured MFs indicated that the true MF for most residences with estimated MF close to zero were obviously underestimated, but still remained under 0.1 μT (the boundary of the reference group in the analysis). Thus, exposure misclassification which existed in this study was not substantial and was unlikely to be differential because blindness was successfully applied to the entire process of exposure assessment. The nondifferential misclassification of exposure should not be a valid argument against the observed significant association between residential MF and leukemia, since bias away from the null resulting from a nondifferential misclassification of exposure does not occur in the upper exposure level in case-control studies with three exposure levels (36). In both excess risk levels (0.1-0.2 μT and >0.2 μT in this study), the elevated risks of leukemia could be the result of a reversal of OR only when exposure classification is worse than chance (36), which is certainly not the case of our data. It was unclear, however, if or by how much the exposure misclassification was responsible for the null relative risk estimates of both brain tumors and female breast cancers.

Two weaknesses were recognized in this study and were in general considered limitations for studies using administrative data which were not routinely collected for specific purposes. One of them was a failure to get complete information on potential confounders through performing an interview with study subjects individually. Partial information concerning these potential confounders were alternatively retrieved from hospital data for study subjects diagnosed in medical centers. We attempted to examine whether these variables were associated with residential MF. Among these variables, SES was of great interest not only because epidemiological studies have reported a weak association of socioeconomic status with brain tumors and a strong association with leukemia and female breast cancers but also because people living near high-voltage transmission lines were suspected of having lower SES on a ground that most transmission lines were located in rural areas. We used education, which is stable in adulthood, as the indicator of SES and found no evidence of an association between education and residential MF. This result agrees with Salzberg et al. in Melbourne, Australia (37) who found only weak association between residential MF and specific aspects of SES and none with combined indices of SES variables. The study of Wartenberg et al. (38) in New Jersey also reported that there was no evidence of disparity with respect to demographic characteristics and SES in population living near high-voltage transmission lines, compared with the general population. It can therefore be assumed that our results were unlikely to have been confounded by SES. For female breast cancers, the reproductive factors did not differ markedly between women with and without elevated residential MF, indicating no confounding effect of these reproductive variables. Diet is another important determinant for female breast cancers. We did not have data to show whether there was an association between residential MF and diet among study subjects.

The other weakness was that we did not contact study subjects or their next of kin to obtain their residential histories. An exposure misclassification may have resulted from ignoring the subject's exposure prior to his/her diagnosis. The extent of exposure misclassification was obviously dependent upon the frequency of moving among study subjects given that the power facilities and consumption had not changed considerably during the study period. The statistics show that the annual frequency of moving in the study area was 5.48 per 100 persons in average between 1983 and 1992 (17). This frequency of moving is low and makes it possible to assume that exposure assessed at time of diagnosis was representative of past exposure for most study subjects. In fact, we examined a scenario which assumed that the annual frequency of moving between 1983 and 1992 was contributed by the entirely different study subjects in order to estimate the maximum number of study subjects who ever moved during the 5-year period prior to his/her diagnosis. It was estimated that some 1,250 study subjects ever moved during the 5-year period prior to diagnosis. Under the assumption that the likelihood of moving is unrelated to residential MF, the scenario gave an agreement level of 0.73 (Kapppa=0.73, 95 percent CI 0.71-0.75) between residential MFs estimated for the year of diagnosis and estimated for the 5-year period before diagnosis.

The results from previous studies of adult leukemia and brain tumors in relation to residential MF are not completely consistent. The end-points varied from all causes of death (11, 15) to acute nonlymphoid leukemia incidence only (12). Following the first residential study of adult cancers reporting a significantly elevated relative risk estimate of nervous system, uterus, breast, and lymphoma for "exposed" adults (10), Severson et al. found that neither were direct measured MF nor wiring codes associated with acute nonlymphoid leukemia (12). On the other hand, Coleman et al. (13) reported an increased 1.5-fold risk of leukemia among people residing within 100 meters of power facilities. Their results were partially supported by Youngson et al. who suggested a small association between myeloid leukemia and residential proximity to overhead lines or estimated MF (14). A recent Swedish study (16) reported no association of time-weighted-average (TWA) MF with total leukemia, but positive associations with AML (relative risk=1.7) and CML (relative risk=1.7) in people living with TWA MF levels $\geqq$ 0.2 $\mu$T. However, the two elevated relative risk estimates were based on 9 and 7 exposed cases and therefore have wide confidence intervals. The relative risk estimates for the CLL and central nervous system tumors were close to null in the analysis by Feychting and Ahlbom (16). Two retrospective cohort studies (11, 15) provided no evidence to support the hypothesis that residential MF will increase the risk of leukemia or brain tumors in adults. In general, the studies by Severson et al. (12) and Feychting and Ahlbom (16) were methodologically superior to the other adult residential studies in terms of exposure assessment and control for confounding. Our results were in general consistent with the findings by some of previous residential studies, suggesting an elevated risk of leukemia (all types) (13, 14). The confidence interval of relative risk estimates suggests that the true excess risk of leukemia can be anywhere between 5 percent and 119 percent for exposure >0.2 μT. Sample size may therefore explain why some previous adult residential studies did not detect an elevated risk of leukemia.

Our analysis showing a slight but not statistically significant association between residential MF and adult brain tumors can be comparable to the null findings of previous studies (11, 15, 16). In addition to residential studies, recent well-designed occupational studies suggested that power frequency MF are associated with the risk of leukemia (3, 4, 39) but the link to brain tumors is much less consistent (3, 4, 7, 40). The relative risk estimates of brain tumors were based on 455 cases and controls, allowing a 50 percent chance of detecting a 50 percent increase in risk at a two-sided $\alpha$ level of 0.05 and an estimated exposure rate among controls of 10 percent. Such power is inadequate to detect a small association and could be responsible for the null risk estimates of brain tumors observed.

To our knowledge, our study was the first one designed to investigate the risk of female breast cancers in relation to residential MF. Three earlier occupational studies (21-23) reported elevated relative risks of breast cancers (6.5 in the study of Matanoski et al. and 2.0 in studies of Demers et al. and Tynes and Anderson) among male workers in occupations with elevated exposure to MF. Five recent studies, on the other hand, did not find this association (4, 6, 40-42). It is, however, difficult to compare these results with ours because the end-points were dissimilar. The studies of female breast cancers in relation to MF were relatively scarce and showed no consistency at all. After adjustment for reproductive variables, age, education and weight, Vena et al. found that the use of electric blanket in a 10-year period prior to diagnosis was unrelated to the risk of breast cancer among postmenopause women (43). A recent occupational study investigating breast cancer mortality among female electrical workers in the United States showed that these workers have experienced a higher risk of breast cancer mortality than other employed women with relative risk estimate of 1.38, 95 percent CI 1.04-1.82 (44). Our study did not discover any significant excess risk of breast cancer among adult females with prolonged exposure to elevated MF at home. Although the relative risk estimate of breast cancer was not adjusted for reproductive variables, social class, and anthropometric measures, additional information have shown a minute likelihood that these known risk factors for female breast cancers may have biased our results. Additionally, our study being based on 1,562 case-control pairs, the power to detect a 50 percent increase in risk, given a 10 percent "exposed" population and a 0.05 significance level, was fairly high. If MF causes female breast cancers, the increased risk must be very small indeed.

Any definite conclusion concerning the causal relationship between power frequency MF and the risks of adult leukemia, brain tumors, or female breast cancers will be considered premature at this time. Our data support the hypothesis that the risk of adult leukemia will increase with prolonged residential exposure to elevated MF, but do not show such a link for brain tumors and female breast cancers. Our analysis also suggests that future studies should be devoted to evaluate whether age or gender may modify the carcinogenic effect, if any, of MF.

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List of Tables and Figures

Table 1. Study groups and participants

| | Leukemia | | Brain tumors | | Female breast cancers | |
|---|---|---|---|---|---|---|
| | cases n (%) | controls n (%) | cases n (%) | controls n (%) | cases n (%) | controls n (%) |
| Study period | 1987-1992 | | 1987-1992 | | 1990-1992 | |
| Cancer register | 1135 (100.00) | 1135 (100.00) | 705 (100.00) | 705 (100.00) | 2407 (100.00) | 2407 (100.00) |
| Elimination due to missing address at diagnosis, missing pathological confirmation, or duplicate registration | 11 (0.97) | 11 (0.97) | 9 (1.28) | 9 (1.28) | 22 (0.91) | 22 (0.91) |
| Unavailability of residential maps | 254 (22.38) | 235 (20.70) | 119 (16.88) | 144 (20.43) | 405 (16.83) | 505 (20.98) |
| Subjects with exposure information | 870 (76.65) | 889 (78.33) | 577 (81.84) | 552 (78.30) | 1980 (82.26) | 1880 (78.11) |
| Participant pairs preserved * | 708 (62.83) | 708 (62.83) | 455 (64.54) | 455 (64.54) | 1562 (64.89) | 1562 (64.89) |
| Participants diagnosed at medical centers † | 320 (28.19) | 311 (27.40) | 183 (25.96) | 203 (28.79) | 612 (25.43) | 659 (27.38) |
| Participants with measured magnetic fields ‡ | 48 (4.23) | 62 (5.46) | 43 (6.10) | 36 (5.11) | 98 (4.07) | 120 (4.99) |

* The pairs preserved were used for testing the underlying hypotheses of the present study.

† These participants were used for an analysis characterizing people with different exposures to residential magnetic fields.

‡ The participants for whom an indoor short-term measurement of magnetic fields was conducted

Table 2. The distributions of matching variables and characteristics of districts in the study area in cases and controls by types of cancer.

| | Leukemia | | Brain tumors | | Female breast cancers | |
|---|---|---|---|---|---|---|
| | Case (%) | Control (%) | Case (%) | Control (%) | Case (%) | Control (%) |
| Age at diagnosis | | | | | | |
| <40 | 270 (38.14) | 270 (38.14) | 188 (41.32) | 188 (41.32) | 396 (25.35) | 396 (25.35) |
| 40-49 | 94 (13.28) | 94 (13.28) | 73 (16.04) | 73 (16.04) | 478 (30.60) | 478 (30.60) |
| 50-59 | 104 (14.69) | 104 (14.69) | 66 (14.51) | 66 (14.51) | 294 (18.82) | 294 (18.82) |
| >59 | 240 (33.90) | 240 (33.90) | 128 (28.13) | 128 (28.13) | 394 (25.22) | 394 (25.22) |
| Sex | | | | | | |
| Male | 417 (58.90) | 417 (58.90) | 249 (54.73) | 249 (54.73) | — | — |
| Female | 291 (41.10) | 291 (41.10) | 206 (45.27) | 206 (45.27) | 1562 (100) | 1562 (100) |
| Year of diagnosis | | | | | | |
| 1987 | 121 (17.09) | 86 (12.15) | 82 (18.02) | 72 (15.82) | — | — |
| 1988 | 106 (14.97) | 98 (13.84) | 75 (16.48) | 58 (12.75) | — | — |
| 1989 | 118 (16.67) | 112 (15.82) | 74 (16.26) | 78 (17.14) | — | — |
| 1990 | 114 (16.10) | 91 (12.85) | 71 (15.60) | 77 (16.92) | 454 (29.07) | 553 (35.40) |
| 1991 | 119 (16.81) | 133 (18.97) | 79 (17.36) | 70 (15.38) | 489 (31.31) | 452 (28.94) |
| 1992 | 130 (18.36) | 188 (26.55) | 74 (16.26) | 100 (21.98) | 619 (39.63) | 557 (35.66) |
| Urbanization* | | | | | | |
| I | 382 (53.95) | 401 (56.64) | 235 (51.65) | 237 (52.09) | 944 (60.44) | 874 (55.95) |
| II | 219 (30.93) | 197 (27.82) | 160 (35.16) | 141 (30.99) | 407 (26.06) | 465 (29.77) |
| III | 107 (15.11) | 110 (15.54) | 60 (13.19) | 77 (16.92) | 211 (13.51) | 223 (14.28) |
| District | | | | | | |
| Taipei city | 355 (50.14) | 359 (50.71) | 216 (47.47) | 216 (47.47) | 842 (53.91) | 799 (51.15) |
| Keelung | 46 (6.50) | 50 (7.06) | 26 (5.71) | 36 (7.91) | 88 (5.63) | 88 (5.63) |
| Taipei county | 257 (36.30) | 44 (34.46) | 182 (40.00) | 163 (35.82) | 530 (33.93) | 553 (35.40) |
| Taoyuan | 50 (7.06) | 55 (7.77) | 31 (6.81) | 40 (8.79) | 102 (6.53) | 122 (7.81) |
| Neighboring industrial parks | | | | | | |
| Yes | 181 (25.56) | 176 (24.86) | 115 (25.27) | 126 (27.69) | 360 (23.05) | 400 (25.61) |
| No | 527 (74.44) | 532 (75.14) | 340 (74.73) | 329 (72.31) | 1202 (76.95) | 1162 (74.39) |
| Total | 708 (100) | 708 (100) | 455 (100) | 455 (100) | 1562 (100) | 1562 (100) |

* Urbanization I indicates the districts most urbanized.

Table 3. Relative risk of leukemia, brain tumors and female breast cancers by residential MF* exposure in the year of diagnosis.

| | <0.1 μT* | | 0.1-0.2 μT | | >0.2 μT | | Test for trend |
|---|---|---|---|---|---|---|---|
| | case | control | case | control | case | control | *p*-value |
| Leukemia | | | | | | | |
| *Estimated MF (average)* | 583 | 617 | 42 | 33 | 83 | 58 | |
| Crude OR* (95% CI*) | 1.00 | | 1.35 (0.82-2.21) | | 1.51 (1.05-2.19) | | |
| Adjusted OR (95% CI)† | 1.00 | | 1.32 (0.82-2.12) | | 1.53 (1.06-2.20) | | 0.013 |
| *Estimated MF (maximum)* | 572 | 603 | 40 | 39 | 96 | 66 | |
| Crude OR (95% CI) | 1.00 | | 1.08 (0.67-1.75) | | 1.53 (1.08-2.17) | | |
| Adjusted OR (95% CI) | 1.00 | | 1.07 (0.68-1.70) | | 1.54 (1.10-2.16) | | 0.015 |
| Brain tumors | | | | | | | |
| *Estimated MF (average)* | 373 | 384 | 19 | 20 | 63 | 51 | |
| Crude OR (95% CI) | 1.00 | | 0.98 (0.49-1.95) | | 1.27 (0.84-1.93) | | |
| Adjusted OR (95% CI) | 1.00 | | 0.98 (0.51-1.89) | | 1.23 (0.82-1.84) | | 0.346 |
| *Estimated MF (maximum)* | 365 | 376 | 22 | 24 | 68 | 55 | |
| Crude OR (95% CI) | 1.00 | | 0.94 (0.50-1.78) | | 1.27 (0.85-1.90) | | |
| Adjusted OR (95% CI) | 1.00 | | 0.93 (0.51-1.86) | | 1.23 (0.83-1.82) | | 0.346 |
| Female breast cancers | | | | | | | |
| *Estimated MF (average)* | 1297 | 1324 | 81 | 78 | 184 | 160 | |
| Crude OR (95% CI) | 1.00 | | 1.06 (0.76-1.48) | | 1.17 (0.93-1.48) | | |
| Adjusted OR (95% CI) | 1.00 | | 1.06 (0.77-1.47) | | 1.17 (0.93-1.47) | | 0.168 |
| *Estimated MF (maximum)* | 1288 | 1308 | 77 | 73 | 197 | 181 | |
| Crude OR (95% CI) | 1.00 | | 1.07 (0.76-1.51) | | 1.11 (0.89-1.38) | | |
| Adjusted OR (95% CI) | 1.00 | | 1.05 (0.75-1.47) | | 1.11 (0.89-1.37) | | 0.348 |

* MF, magnetic fields; μT, micro-Tesla; OR, odds ratio; CI, confidence intervals

† Adjusted OR was derived from the conditional maximum likelihood estimate of regression coefficients by adjusting matching variables, urbanization and neighboring industrial parks.

Table 4. Age-specific relative risk* of leukemia, brain tumors and female breast cancers by residential MF† exposure in the year of diagnosis.

| | <0.1 μT† | | 0.1-0.2 μT | | >0.2 μT | |
|---|---|---|---|---|---|---|
| | case | control | case | control | case | control |
| Leukemia | | | | | | |
| *Age ≤ 47‡* | 285 | 300 | 23 | 21 | 40 | 26 |
| Crude OR† (95% CI†) | 1.00 | | 1.15 (0.60-2.22) | | 1.62 (0.94-2.81) | |
| Adjusted OR (95% CI)§ | 1.00 | | 1.10 (0.59-2.05) | | 1.57 (0.91-2.72) | |
| *Age >47* | 298 | 317 | 19 | 12 | 43 | 32 |
| Crude OR (95% CI) | 1.00 | | 1.68 (0.76-3.76) | | 1.43 (0.86-2.39) | |
| Adjusted OR (95% CI) | 1.00 | | 1.68 (0.79-3.60) | | 1.38 (0.84-2.27) | |
| Brain tumors | | | | | | |
| *Age ≤ 47* | 211 | 209 | 10 | 6 | 26 | 26 |
| Crude OR (95% CI) | 1.00 | | 1.65 (0.54-5.21) | | 0.99 (0.54-1.83) | |
| Adjusted OR (95% CI) | 1.00 | | 1.66 (0.60-4.60) | | 0.99 (0.56-1.76) | |
| *Age >47* | 162 | 175 | 9 | 14 | 37 | 25 |
| Crude OR (95% CI) | 1.00 | | 0.69 (0.27-1.76) | | 1.60 (0.89-2.86) | |
| Adjusted OR (95% CI) | 1.00 | | 0.67 (0.28-1.62) | | 1.49 (0.83-2.66) | |
| Female breast cancers | | | | | | |
| *Age ≤ 47* | 661 | 660 | 39 | 39 | 93 | 88 |
| Crude OR (95% CI) | 1.00 | | 1.00 (0.62-1.61) | | 1.06 (0.76-1.46) | |
| Adjusted OR (95% CI) | 1.00 | | 0.99 (0.61-1.61) | | 0.99 (0.72-1.37) | |
| *Age >47* | 636 | 664 | 42 | 39 | 91 | 72 |
| Crude OR (95% CI) | 1.00 | | 1.12 (0.70-1.80) | | 1.32 (0.94-1.86) | |
| Adjusted OR (95% CI) | 1.00 | | 1.08 (0.68-1.73) | | 1.40 (0.99-1.97) | |

* The relative risk estimates were based on the magnetic fields calculated from annual average current.

† MF, magnetic fields; μT, micro-Tesla; OR, odds ratio; CI, confidence intervals

‡ Median age of controls from three study groups

§ Adjusted OR was derived from the conditional maximum likelihood estimate of regression coefficients by adjusting matching variables, urbanization and neighboring industrial parks.

Table 5. Sex-specific relative risk* of leukemia and brain tumors by residential MF† exposure in the year of diagnosis.

| | <0.1 μT† | | 0.1-0.2 μT | | >0.2 μT | |
|---|---|---|---|---|---|---|
| | case | control | case | control | case | control |
| Leukemia | | | | | | |
| *Male* | 343 | 366 | 26 | 20 | 48 | 31 |
| Crude OR† (95% CI†) | 1.00 | | 1.39 (0.73-2.64) | | 1.65 (1.00-2.73) | |
| Adjusted OR (95% CI)‡ | 1.00 | | 1.38 (0.76-2.52) | | 1.71 (1.04-2.82) | |
| *Female* | 240 | 251 | 16 | 13 | 35 | 27 |
| Crude OR (95% CI) | 1.00 | | 1.29 (0.57-2.91) | | 1.36 (0.77-2.39) | |
| Adjusted OR (95% CI) | 1.00 | | 1.26 (0.59-2.70) | | 1.33 (0.79-2.23) | |
| Brain tumors | | | | | | |
| *Male* | 198 | 205 | 12 | 10 | 39 | 34 |
| Crude OR (95% CI) | 1.00 | | 1.24 (0.49-3.18) | | 1.19 (0.70-2.02) | |
| Adjusted OR (95% CI) | 1.00 | | 1.24 (0.53-2.88) | | 1.19 (0.72-1.96) | |
| *Female* | 175 | 179 | 7 | 10 | 24 | 17 |
| Crude OR (95% CI) | 1.00 | | 0.72 (0.24-2.10) | | 1.44 (0.72-2.92) | |
| Adjusted OR (95% CI) | 1.00 | | 0.67 (0.25-2.04) | | 1.46 (0.74-2.89) | |

* The relative risk estimates were based on the magnetic fields calculated from annual average current.

† MF, magnetic fields; μT, micro-Tesla; OR, odds ratio; CI, confidence intervals

‡ Adjusted OR was derived from the conditional maximum likelihood estimate of regression coefficients by adjusting matching variables, urbanization and neighboring industrial parks.

Table 6. Characteristics of study subjects living with different levels MF* emitted from transmission lines (N=2,288)†

| | Residential MF at cancer diagnosis | | |
|---|---|---|---|
| | <0.1 μT* | 0.1-0.2 μT | >0.2 μT |
| Sex | | | |
| Male (%) | 503 (25.97) | 34 (30.63) | 66 (27.50) |
| Female (%) | 1434 (74.03) | 77 (69.37) | 174 (72.50) |
| Age at diagnosis | | | |
| Mean (SE*) | 46.85 (0.31) | 46.66 (1.36) | 49.04 (0.90) |
| Height at diagnosis (Cm*) | | | |
| Mean (SE) | 159.22 (0.17) | 159.71 (0.73) | 159.64 (0.49) |
| Weight at diagnosis (Kg*) | | | |
| Mean (SE) | 57.92 (0.22) | 59.30 (0.93) | 58.77 (0.62) |
| Education | | | |
| Illiteracy (%) | 272 (14.04) | 13 (11.71) | 26 (10.83) |
| Elementary school (%) | 590 (30.46) | 38 (34.23) | 80 (33.33) |
| High school (%) | 581 (29.99) | 26 (23.42) | 69 (28.75) |
| Professional education or college (%) | 494 (25.50) | 34 (30.63) | 65 (27.08) |
| Smoking | | | |
| Ever (%) | 347 (17.91) | 23 (20.72) | 46 (19.17) |
| Never (%) | 1590 (82.09) | 88 (79.28) | 194 (80.83) |
| Medical X-ray exposure‡ | | | |
| Ever (%) | 350 (18.07) | 12 (10.81) | 42 (17.50) |
| Never (%) | 1587 (81.93) | 99 (89.19) | 198 (82.50) |
| Age at menarche | | | |
| <13 (%) | 89 (9.57) | 5 (9.62) | 9 (7.89) |
| ≥ 13 (%) | 841 (90.43) | 47 (90.38) | 105 (92.11) |
| Menopause | | | |
| Yes (%) | 415 (44.62) | 27 (51.92) | 53 (46.49) |
| No (%) | 515 (55.38) | 25 (48.08) | 61 (53.51) |
| Self-reported irregular period | | | |
| Yes (%) | 168 (18.06) | 11 (21.15) | 16 (14.04) |
| No (%) | 762 (81.94) | 41 (78.85) | 98 (85.96) |
| Number of birth | | | |
| 0 (%)§ | 101 (10.86) | 4 (7.69) | 12 (10.53) |
| 1-2 (%) | 339 (36.45) | 13 (25.00) | 46 (40.35) |
| 3-4 (%) | 374 (40.22) | 28 (53.85) | 38 (33.33) |
| ≥ 5 (%) | 116 (12.47) | 7 (13.46) | 18 (15.79) |
| Age at first labor | | | |
| <21 (%) | 114 (12.26) | 11 (21.15) | 13 (11.40) |
| 21-30 (%) | 635 (68.28) | 34 (65.38) | 82 (71.93) |
| >30 (%) | 80 (8.60) | 3 (5.77) | 7 (6.14) |
| Nulliparity | 101 (10.86) | 4 (7.69) | 12 (10.53) |
| Breast feeding | | | |
| Yes (%) | 656 (70.54) | 41 (78.85) | 89 (78.07) |
| No (%)¶ | 274 (29.46) | 11 (21.15) | 25 (21.93) |

* MF, magnetic fields; μT, micro-Tesla; SE, standard error; Cm, centimeter; Kg, Kilogram.
† Information on reproductive variables were available for only 1,096 subjects diagnosed at gynecological departments.
‡ Chest X-ray was excluded.
§ Unmarried subjects were included.
¶ Nulliparity was included.

Title of Manuscript III

A validity analysis of residential magnetic fields estimated from power information of high-voltage transmission lines

## ABSTRACT

Between November 1994 and May 1995, indoor power frequency magnetic fields (MF) of 407 residences in northern Taiwan were assessed by short-term on site measurements and by modeling power information from high-voltage transmission lines. The study residences were selected according to the distance from the transmission lines with cutoff points of 50 meters (m), 100 m, and 150 m, which gave rise to four groups of residences. The analysis showed that the measured MF were in general higher than the estimated MF, especially among the residences with lower measured MF. The measured and estimated MFs showed an agreement of 0.93 (intra-class correlation coefficient, ICC = 0.93) for the residences within 50 m of the transmission lines. The ICC declined with the distance from the transmission lines with a lowest ICC of 0.42 for the residences located more than 149 m away from the lines. When both measured and estimated MFs were categorized into three levels with cutoff points of 1 milligauss (mG) and 2 mG, the indices of agreement were very similar for the three residential groups within 150 m of the lines with Kappa (K) between 0.51 and 0.55. The K for the residences more than 149 m away from the lines was low at 0.29. The ICC and K observed from a reduced sample of 114 residences presumably representative of all residences in northern Taiwan with respect to the distribution of residential MF was 0.90 and 0.64, respectively. Generalization of the

results from this analysis must be cautious, since ICC and K are determined not only by measurement errors but also by the distribution of residential MF in the study area. They are likely to vary from one study to another, with the measurement error remaining unchanged.

Key words: EMF exposure, magnetic fields, measurement, modeling, Taiwan.

INTRODUCTION

There has been growing concern regarding the carcinogenic effects of environmental exposure to weak time-varying MF, particularly those in the power frequency range (50-60 Hertz (Hz)). Because MF are not seen by the exposed individual and therefore cannot be recalled, the strength of MF can only be documented through on site measurements in the environment. Among epidemiological studies which investigated cancer risks in association with residential MF, a variety of methods have been used to assess MF in the home environment. These methods included wire configurations in the neighborhood of households (Wertheimer and Leeper (1979); Fulton et al. (1980); Kaune et al. (1987); Severson et al. (1988); Savitz et al. (1988); London et al. (1991)), the lateral distance from power lines (Tomenius (1986); McDowall (1986); Coleman et al. (1989); Lin and Lu (1989); Myers et al. (1990); Youngson et al. (1991); Feychting and Ahlbom (1993)), indoor spot or/and 24-hour on site measurements (Tomenius (1986); Severson et al. (1988); Savitz et al. (1988); Coleman et al. (1989); London et al. (1991); Feychting and Ahlbom (1993, 1994)), modeling household MF from power information (Coleman et al. (1989); Myers et al. (1990); Olsen et al. (1992); Feychting and Ahlbom (1993, 1994); Verkasalo et al. (1993)), and the use of portable dosimeters for personal measurements (Kaune et al. (1994); Kavet et al. (1994)). Among these methods, indoor or personal measurements with dosimeters are considered the finest. However, dosimeters have not been widely used in previous studies since a fair number of dosimeters are usually needed in epidemiological studies and it is not feasible to monitor household MF for an aetiologically relevant time period which could be as long as several years. Moreover, the exposure in the recent or remote past, which would be assessed by the retrospective study, is unable to be determined by on site measurements. These disadvantages lead to the use of surrogate methods alternatively in many residential studies. Although some surrogate methods, for example, wire codes, have been argued to be more effective than short-term on site measurements in estimating a long-term exposure (Savitz et al. (1988); London et al. (1991)), they generally have not been validated extensively and empirically.

Previous studies have shown a weak association between wire codes and short-term MF dosimetry (Barnes et al. (1989); London et al. (1991); Kaune et al. (1994)). Therefore, an association found between wire codes and human cancers in many studies barely provides evidence linking MF and human cancers. Compared with wire codes and distance from power lines, MF estimated from power information appears to be more reliable in providing direct estimate of MF exposure. The present study compared residential MF estimated from power information of 69/161/345 kilovolts (kV) transmission lines with those measured by dosimeters in an attempt to evaluate the validity of using currents and other power information to predict MF in the home environment.

## METHODS

### Study residences

Indoor MF of 407 residences were assessed by on site measurements with dosimeters and by modeling power information of high-voltage transmission lines (69/161/345 kV). These residences were occupied by a sample of cancer patients at the time of diagnosis from a registry-based case-control study with 5450 subjects [1]. All study residences were located within four administrative districts of northern Taiwan. The study residences were sampled according to their locations from the transmission lines with cutoff points of 50 meters (m), 100 m, and 150 m. Specifically, 5,450 residences were first categorized into four groups with the lateral distance from the transmission lines of <50 m, 50-99 m, 100-149 m, and ≧ 150 m, respectively. In each group, the residences near the College of Public Health of National Taiwan University (CPHNTU) or the Power Research Institute of Taiwan Power Company (PRITPC), the two institutes involved in the exposure assessment, were visited for indoor MF measurements on a voluntary basis. Between November 1994 and May 1995, MF measurements were carried out for 407 residences. Of them, 97 (23.83%) were within 50 m of the transmission lines, 133 (32.68%) were somewhere between 50 m and 99 m, 87 (21.38%) were between 100 m and 149 m, and 90 (22.11%) were at least 150 meters away from the transmission lines.

Because the distance between a residence and nearby transmission lines is one of the most important determinants of MF, it is clear that the 407 residences as a whole should not be

[1] Li CY, Theriault G, Lin RS. Long-term residential exposure to 60 Hz magnetic fields and risks of adult cancers in Taiwan. (Submitted for publication)

considered a representative sample of the entire residences in northern Taiwan with respect to the underlying distribution of MF. In other words, the agreement between measured and estimated MFs based on the 407 residences does not necessarily reflect the agreement estimated from the entire residences, since the extent of agreement relies not only on the measurement error but also on the distribution of MF among selected residences (Armstrong et al. (1992)). It has shown that, between 1987 and 1992, 8.51% of the residences in northern Taiwan were located within 50 m of the transmission lines, 6.94% were between 50 m and 99 m, 5.54 % were between 100 m and 149 m, and 79.01% were located in an area which was at least 151 m away from the transmission lines [1]. Based upon the above probability distribution, the 407 residences were reduced by stratified random sampling to a sample presumably representative of the entire residences in northern Taiwan with respect to the distribution of MF. The reduced sample comprised 114 residences in which 10 (8.77%) were within 50 m of the transmission lines, 8 (7.02%) were between 50 m and 99 m, 6 (5.26%) were between 100 m and 149 m, and 90 (78.95%) were more than 149 m from the lines.

Measured magnetic fields

All on site measurements were carried out by three investigators from CPHNTU between November 1994 and May 1995. Measurements were performed with EMDEX II (the *EMDEX Electric and Magnetic Field Digital Exposure System*) which is a hardware and software package designed for measuring, recording, and analyzing MF at broadband frequency between 40 and 800 Hz (Silva (1993)). The EMDEX II is a programmable data-acquisition dosimeter that measures the x, y, z vector components of the MF and the resultant MF ($\sqrt{x^2+y^2+z^2}$). Measurements are stored in the meter's memory and later can be transferred through a serial communication port to a computer for storage, display and analysis. All measurements were performed by following a standardized procedure. In summary, once residential occupants accepted the request for indoor measurements, the investigator carried out the measurements at an indoor one-meter-high location nearest to the external transmission lines. The measurement was conducted over approximately 30 to 40 minutes with sampling time interval of 30 seconds. There were roughly 70 readings in average for each residence. The investigator also recorded the time period of measurements in order to retrieve contemporary information of currents from either power generation plants or substations, which was used to calculate the estimated MF at the time of measurements. To minimize the contamination by other sources of MF, the residents were asked to turn the whole household power off (low-power condition) or at least appliances near to the location in which the measurement was conducted during the measurements. More than 70% of the residences were measured under the low-power condition. All the visits were made during the day in order to maximize the resident's compliance. The data recorded from the residential dosimetry were later analyzed at the CPHNTU. The arithmetic mean of all readings (resultant MF) was considered the summary index of MF for each residence and was compared with the MF estimated from relevant power information.

Estimated magnetic fields

In addition to measured MF, MF calculated from currents and other power information were also estimated for the study residences. The 60 Hz MF were calculated, using a computer software (MAGFLD 2.0) (Olsen et al. (1994)), for each residence based on the currents at the time of on site measurements. The calculation considered the external high-voltage transmission lines as the only source of 60 Hz MF. Power information and the distance from the transmission lines are two essential elements for the calculation. Power information included wire geometric configurations, phase in degrees for each conductor, amplitude of current in amperes on the lines, maximum net current through earth as a percentage of the average current, and the geographical resistivity of earth (ohm-meters, $\Omega$ m) in the study area. The other information required for MF calculation is the coordinate of each residence in relation to the transmission lines, which included the lateral distance from the transmission lines (X-axis) and the height above the ground (Y-axis).

Power information was furnished by the Department of Transmission and Substation Project (DTSP), a technical institute affiliated with Taiwan Power Company (TPC). All power information remained constant over the period within which on site measurements were conducted except the load on the lines. The load on the lines is routinely monitored and recorded on an hourly basis by either power generation plants or power substations. Determination of the lateral distance between the transmission lines and each residence was accomplished stepwise. First, each residence was inscribed on a large-scaled residential map showing individual street and residential locations. Because the residences extended over 31 administrative districts whose residential maps were not standardized, a series of residential maps with distinguishable scales were used to locate the residences. The scale of residential maps ranged from 1 in 5300 (1.89 mm = 10 m) to 1 in 10000 (1.00 mm = 10 m). Second, utility route maps, which displayed the transmission lines in the 31 administrative districts, were generated from the pre-computerized utility maps of the DTSP to individually and exactly fit the 31 residential maps in scales. With residential and utility route maps identical in scale, it was possible to determine the lateral distance of each residence to the nearby transmission lines. Because the design and construction of buildings were not similar and there were no efficient ways of knowing exactly the altitude of each residence, we simply used three meters to estimate the distance between two floors within a building. The MF were estimated for a location one meter above the floor for each residence.

Statistical Analyses

The primary purpose of this study is to evaluate the extent of agreement between measured and estimated MFs. The measured MF was considered a "gold standard" in comparison with the estimated MF.

Two measures of agreement were used: the "intra-class correlation coefficient (ICC)" (Streiner and Norman (1989)) and "Cohen's Kappa (K)" (Cohen (1960)). The ICC was applied to measure the agreement when both measured and estimated MFs were taken as continuous variables. On the other hand, the K was used for categorical MFs, with three levels, "low" representing <1 milligauss (mG), "moderate" representing 1 mG - 2 mG and "high" representing >2 mG. The ICC , using analysis of variance (ANOVA) to determine the components of variance of MF, was presented as the ratio of variance between residences (true variation) to the summation of error variance and true variance. Several studies have used 2 mG as a cutoff point to define broad categories of MF exposure (Savitz et al. (1988); London et al. (1991); Feychting and Ahlbom (1993, 1994)). Below this level, subjects are considered "unexposed", and above this level they are considered "exposed". We attempted to use three levels of MF with cutoff points of 1 mG and 2 mG in this analysis. Because K is a measure of exact agreement with all disagreements considered to be equally serious (Cohen (1960)), the use of K is not appropriate, in certain circumstances, when the measurement of interest is an ordered categorical variable (Armstrong et al. (1992)). In addition to K, we therefore used weighted Kappa (K*w*) which gives a partial credit to a close but not exact agreement (Cohen (1968)) in order to measure partial agreement. The confidence intervals for K and K*w* can be computed based on the large sample estimate of the standard error of K and K*w* (Armstrong et al. (1992)).

RESULTS

The distributions of measured and estimated MFs of 407 residences are presented in Table 1. The coefficient of variance (CV) of measured MF for each of the four residential groups was slightly different with the largest value (98.65) for the residences located between 50 and 99 m. The CV of estimated MF, on the other hand, was large for the residences $\geqq$ 150 meters (223.53). The CV of estimated MF for the reduced sample was almost twice as large as that of measured MF (207.94 Vs 111.60). The difference between the largest and smallest measured MFs was very large (21.35 mG) among the residences <50 m, as compared to that among other residential groups. Similar findings were also observed for estimated MF. The larger range was mainly because some residences within 50 m of the transmission lines have experienced dramatically high MF. It was noted that the smallest measured MF among the entire residences was 0.17 mG, whereas the estimated MF for more than a quarter of residences $\geqq$ 150 meters were estimated to be very close to zero. The findings suggested that the background MF in northern Taiwan was about 0.2 mG, which was contributed from power sources other than the transmission lines.

As shown in Table 1, there was a reasonable tendency that the distance from the transmission lines tended to have influence on the magnitude of measured MF. Without performing statistical testing, the residences close to the transmission lines appeared to experience higher measured MF, and the mean of measured MF declined with the distance from the transmission lines. The trend observed in measured MF was also evident for estimated MF. Additionally, the mean of measured MF was constantly greater than that of estimated MF across all residential groups. It suggested an underestimation by MF estimated from power information of the transmission lines, which was graphically substantiated by comparing the measured MF with estimated MF of each residence individually (Figure 1). Figure 1 shows the deviation which was defined by the ratio of the difference between measured and estimated MFs to the measured MF. Measured MF were in general higher than estimated MF in most of the residences, particularly among the residences with measured MF lower than 0.5 mG. It was also noted from Figure 1 that the agreement between measured and estimated MFs appeared to improve for the residences with measured MF higher than 2 mG.

The components of variance in MF and the values of ICC are presented in Table 2. The variance between residences (true variance) was prominent (14.88 mG) for the residences within 50 m of the transmission lines. Along with a small variance due to residual error, the ICC was estimated to be 0.93 for the residential group nearest to the transmission lines. The ICC declined rapidly with increase in distance with lowest ICC of 0.42 for the residences located ≧ 150 m from the lines. Among the residences ≧ 150 m, the variance due to residences (0.11 mG) was even less than the residual variance (0.15 mG), which resulted in an ICC below 0.5. The ICC for the reduced sample was also high (ICC = 0.90), suggesting a reasonable agreement between MFs resulting from on site measurements and those derived from calculations for a representative sample of northern Taiwan residences.

Table 3 shows the categorized data for both measured and estimated MFs. The proportions of underestimation of MF by calculating power information for the residential groups <50 m, 50-99 m, 100-149 m, and ≧ 150 m were 7.2%, 27.1%, 14.9%, and 15.6%, respectively. The proportions of overestimation, however, were much less than that of underestimation for each of the residential groups except the residences within 50 m of transmission lines. The proportions of underestimation and overestimation for the reduced sample were 14.0% and 2.6%, respectively. The K for the residences in the group <50 m was 0.51 (95% CI = 0.29-0.73). A similar K was also observed for the two groups between 50 and 149 m (0.53, 95% CI = 0.41-0.65 for 50 - 99 m and 0.55, 95% CI = 0.39-0.71 for 100 - 149 m) (Table 4). For the residences ≧ 150 m, the K dropped dramatically to 0.29 (95% CI = 0.05-0.53). The K for the reduced sample was of 0.64 (95% CI = 0.50-0.78).

When a partial weight of 0.5 was assigned to a close but not exact agreement, the agreement, expressed by Kw, was again similar for the two residential groups within 100 m of the transmission lines (Kw = 0.60 ,95% CI = 0.42-0.78 for <50 m and Kw = 0.60, 95% CI = 0.50-0.70 for 50 - 99 m) (Table 5). The Kw for the residences ≧ 150 m was still low (Kw = 0.33, 95% CI = 0.13-0.53). The Kw for the reduced sample increased by 12.5% from 0.64 to 0.72 (95% CI = 0.62-0.82). The agreement based on the categorical data also declined with the increasing distance from the transmission lines.

## DISCUSSION

The measured MF in the present study presumably came exclusively from external electric power sources, such as transmission, distribution, and substation equipment, since all measurements were conducted in a situation where the household power or at least major appliances were turned off. The estimated MF, on the other hand, considered only the MF emitted from high-voltage transmission lines. Not surprisingly, the residences close to the transmission lines tended to show a higher estimated MF, since the distance from the lines is one of the most important elements in the equation to calculate MF (Olsen et al. (1994)). The negative association between measured MF and the distance from the transmission lines was also observed in this analysis, which suggested that the previous studies using the distance from power lines to estimate residential MF were justifiable at least to some extent.

The agreement between measured and estimated MFs appeared to be better, though not statistically significant, for the residential groups located near the transmission lines. Two indices, ICC and K, consistently indicated that modeling power information to estimate MF was not precise for the residences in locations which were distant from the transmission lines. Based on the analysis of the reduced sample, there was an excellent agreement for continuous data (ICC = 0.90). The agreement was much lower (K=0.64) for categorical data with cutoff points of 1 mG and 2 mG, suggesting a possibility that exposure misclassification may have occurred in previous epidemiological studies which used power information to assess MF exposure. The increase in overall agreement after considering the partial agreement indicated that some estimated MF missed exact prediction by only one exposure category.

Our data showed that the magnitude of estimated MF was lower than that of measured MF for most residences irrespective of their locations. However, the magnitude of deviation of estimated MF from measured MF for individual residence was neither systematic nor predictable. The underestimation by modeling power information of the transmission lines was likely due to an incomplete consideration of MF sources other than transmission lines, such as distribution lines and transformers. Additionally, because the EMDEX II meter can receive the signals with frequencies ranging from 40 to 800 Hz, and the model considers only 60 Hz MF in the calculation, the harmonic fields that accompanied the 60 Hz MF from distribution lines (the harmonic content for transmission lines is practically zero) could have contributed to the underestimation as well. It was noted that the smallest value of measured MF among all study residences was 0.17 mG, which suggested that the external sources of MF other than transmission lines may have contributed some 0.2 mG to the residential MF in the study area.

It was of interest to observe that the deviation of estimated MF from measured MF appeared to be smaller for the residences with higher measured MF, say 2 mG. Because most of the residences with measured MF of 2 mG or more were near transmission lines, a possible explanation of the above findings was that MF of these residences were mainly a function of nearby transmission lines and to a much lesser extent of distribution lines supplying these residences. Specifically, our findings may suggest that the transmission lines would outweigh the distribution line in determining the MF of the residences located near the transmission lines. For the residences far away from the transmission lines, on the other hand, MF might be contributed by the transmission and distribution lines with equal weight or even with greater weights from the distribution line. It is known that currents in a transmission line can be a dominant source of MF in a home located near the right of way, even though the distance from the transmission lines may be greater than that from the distribution lines supplying the residence.

It should be recalled that the two indices of agreement, K and ICC, are not only influenced by measurement errors but also by the distribution of true residential MF (measured MF in the present study) among study residences. Even if the instrument used for measurements had the same error variance in the two populations, the measures of K and ICC would be smaller in the population with least variation in true exposure (Armstrong et al. (1992)). Therefore, the differences in ICC, K, and K*w* between residential groups were not completely attributable to the measurement error, since the variance in measured MF was not the same among residential groups. The use of these coefficient to express measurement error has been criticized (Altman and Bland (1983)). Although measurement errors due to modeling power information were recognized in the analysis, we were not capable of drawing any firm conclusion, based on our data, concerning the association between measurement errors and the distance from the transmission lines.

According to this analysis, the use of power information to estimate categorical residential MF was subject to exposure misclassification. Given an agreement level of 0.64, a question emerged as to whether modeling power information from major power lines may be used to determine the residential MF in future epidemiological studies. The answer is apparently beyond the issue of measurement validity. The selection of exposure assessment methods in epidemiological studies might have other "logical" or "practical" considerations, albeit the validity is unequivocally the most important one. Easy implementation is one of the most important reasons for surrogate methods to be used in the epidemiological study which usually requires a fair number of study subjects and long-term monitor of MF exposure. However, it should keep in mind that a lack of satisfactory validity will compromise any strength of the exposure assessment methods and lead to an invalid risk estimates. It is therefore suggested that a careful evaluation of validity for any surrogate method which has been and will be used in the epidemiological studies should be seriously considered.

The use of power information to estimate residential MF has several advantages. First, it provides a more direct measure of MF exposure than the other two frequently used methods , i.e., wire configuration and distance from power lines. Additionally, MF are theoretically predictable, since, unlike electric fields, MF are not shielded by electrically conductive materials and will penetrate buildings, trees, and organism (Kaune et al. (1982)). Second, based on the routinely recorded current load of major power lines, the approach can be used efficiently to assess MF for a large number of study subjects over a long period of time. Third, the completeness of records makes it possible to estimate the MF in the remote past, which is very helpful for retrospective studies. Although our analysis suggested a possible exposure misclassification resulting from using exclusively power information of the transmission lines to characterize residential MF, modeling power information can still be considered a good alternative for on site measurements in future studies. Meanwhile, our analysis is also suggestive that more efforts should be devoted to improve the techniques of modeling power information through a thorough consideration of all possible MF sources.

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Table 1. Distributions [a] of measured and estimated MFs (mG) of 407 residences by lateral distance from the transmission lines.

| Lateral Distance (m) | N | Min. | Q1 | Med. | Q3 | Max. | Mean | S.D. | C.V. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *Measured MF* | | | | | |
| 0-49 | 97 | 0.78 | 3.02 | 4.30 | 6.42 | 22.13 | 5.36 | 4.05 | 75.56 |
| 50-99 | 133 | 0.51 | 1.13 | 1.65 | 2.41 | 14.32 | 2.23 | 2.20 | 98.65 |
| 100-149 | 87 | 0.31 | 0.72 | 0.93 | 1.31 | 3.12 | 1.12 | 0.61 | 54.46 |
| ≧ 150 | 90 | 0.17 | 0.34 | 0.48 | 0.82 | 3.12 | 0.73 | 0.61 | 83.56 |
| Reduced sample | 114 | 0.17 | 0.39 | 0.64 | 1.40 | 7.11 | 1.08 | 1.21 | 111.60 |
| | | | | *Estimated MF* | | | | | |
| 0-49 | 97 | 0.81 | 2.86 | 3.97 | 6.11 | 20.64 | 5.09 | 3.93 | 77.21 |
| 50-99 | 133 | 0.15 | 0.95 | 1.49 | 2.00 | 9.76 | 1.77 | 1.36 | 76.84 |
| 100-149 | 87 | 0.09 | 0.21 | 0.59 | 1.14 | 2.51 | 0.76 | 0.62 | 81.58 |
| ≧ 150 | 90 | 0.00 | 0.01 | 0.05 | 0.11 | 2.03 | 0.17 | 0.38 | 223.53 |
| Reduced sample | 114 | 0.00 | 0.02 | 0.08 | 0.80 | 8.53 | 0.63 | 1.31 | 207.64 |

[a] N, number of study residences; Min., minimum, Q1=25% percentile; Med., median; Q3=75 percentile; Max., maximum; SD=standard deviation; CV= coefficient of variance

Table 2. Analysis of variance and Intra-class Correlation Coefficients (ICC) by lateral distance from the transmission lines.

| Lateral Distance (m) | Variance components (mG) | | | ICC |
| --- | --- | --- | --- | --- |
| | Between instruments [a] | Between residences | Residual error | |
| 0-49 | 0.03 | 14.88 | 1.01 | 0.93 |
| 50-99 | 0.10 | 2.58 | 0.76 | 0.77 |
| 100-149 | 0.06 | 0.26 | 0.12 | 0.68 |
| $\geqq$ 150 | 0.15 | 0.11 | 0.15 | 0.42 |
| Reduced sample | 0.10 | 1.43 | 0.16 | 0.90 |

[a] Dosimeter and computer software

Table 3. Categorical data of measured and estimated MFs for 407 study residences with cutoff points of 1 and 2 mG by lateral distance from the transmission lines.

| *Measured MF* | *Estimated MF* Low [a] | Moderate [a] | High [a] | Total |
|---|---|---|---|---|
| 0-49 m | | | | |
| Low | 1 | 2 | 0 | 3 |
| Moderate | 2 | 4 | 2 | 8 |
| High | 0 | 5 | 81 | 86 |
| Total | 3 | 11 | 83 | 97 |
| 50-99 m | | | | |
| Low | 22 | 5 | 0 | 27 |
| Moderate | 12 | 39 | 2 | 53 |
| High | 3 | 19 | 31 | 53 |
| Total | 37 | 63 | 33 | 133 |
| 100-149 m | | | | |
| Low | 48 | 5 | 1 | 54 |
| Moderate | 6 | 16 | 1 | 23 |
| High | 3 | 4 | 3 | 10 |
| Total | 57 | 25 | 5 | 87 |
| ≧ 150 m | | | | |
| Low | 71 | 1 | 0 | 72 |
| Moderate | 10 | 3 | 1 | 14 |
| High | 2 | 2 | 0 | 4 |
| Total | 83 | 6 | 1 | 90 |
| Reduced sample | | | | |
| Low | 76 | 2 | 0 | 78 |
| Moderate | 11 | 9 | 1 | 21 |
| High | 2 | 3 | 10 | 15 |
| Total | 89 | 14 | 11 | 114 |

[a] Low, $<$ 1 mG; Moderate, 1 - 2 mG; and High $>$ 2 mG.

Table 4. Kappa (K) for each category of Table 3.

| Lateral Distance (m) | N [a] | Po [b] | Pe [c] | K [d] | S.E.[e](K) | 95% CI [f] for K |
|---|---|---|---|---|---|---|
| 0-49 | 97 | 0.89 | 0.77 | 0.51 | 0.11 | 0.29-0.73 |
| 50-99 | 133 | 0.69 | 0.34 | 0.53 | 0.06 | 0.41-0.65 |
| 100-149 | 87 | 0.77 | 0.49 | 0.55 | 0.08 | 0.39-0.71 |
| $\geqq$ 150 | 90 | 0.82 | 0.75 | 0.29 | 0.12 | 0.05-0.53 |
| Reduced sample | 114 | 0.83 | 0.54 | 0.64 | 0.07 | 0.50-0.78 |

[a] Number of residences

[b] The overall proportion of observed agreement

[c] the overall proportion of chance-expected agreement.

[d] kappa

[e] standard error

[f] confidence interval

Table 5. Weighted Kappa (Kw) for each category of Table 3.

| Lateral Distance (m) | N [a] | Po [b] | Pe [c] | Kw [d] | S.E.[e](Kw) | 95% CI [f] for Kw |
|---|---|---|---|---|---|---|
| 0-49 | 97 | 0.94 | 0.90 | 0.60 | 0.09 | 0.42-0.78 |
| 50-99 | 133 | 0.83 | 0.59 | 0.60 | 0.05 | 0.50-0.70 |
| 100-149 | 87 | 0.86 | 0.69 | 0.56 | 0.08 | 0.40-0.72 |
| ≧ 150 | 90 | 0.89 | 0.85 | 0.33 | 0.10 | 0.13-0.53 |
| Reduced sample | 114 | 0.91 | 0.67 | 0.72 | 0.05 | 0.62-0.82 |

[a] Number of residences

[b] The overall proportion of observed agreement

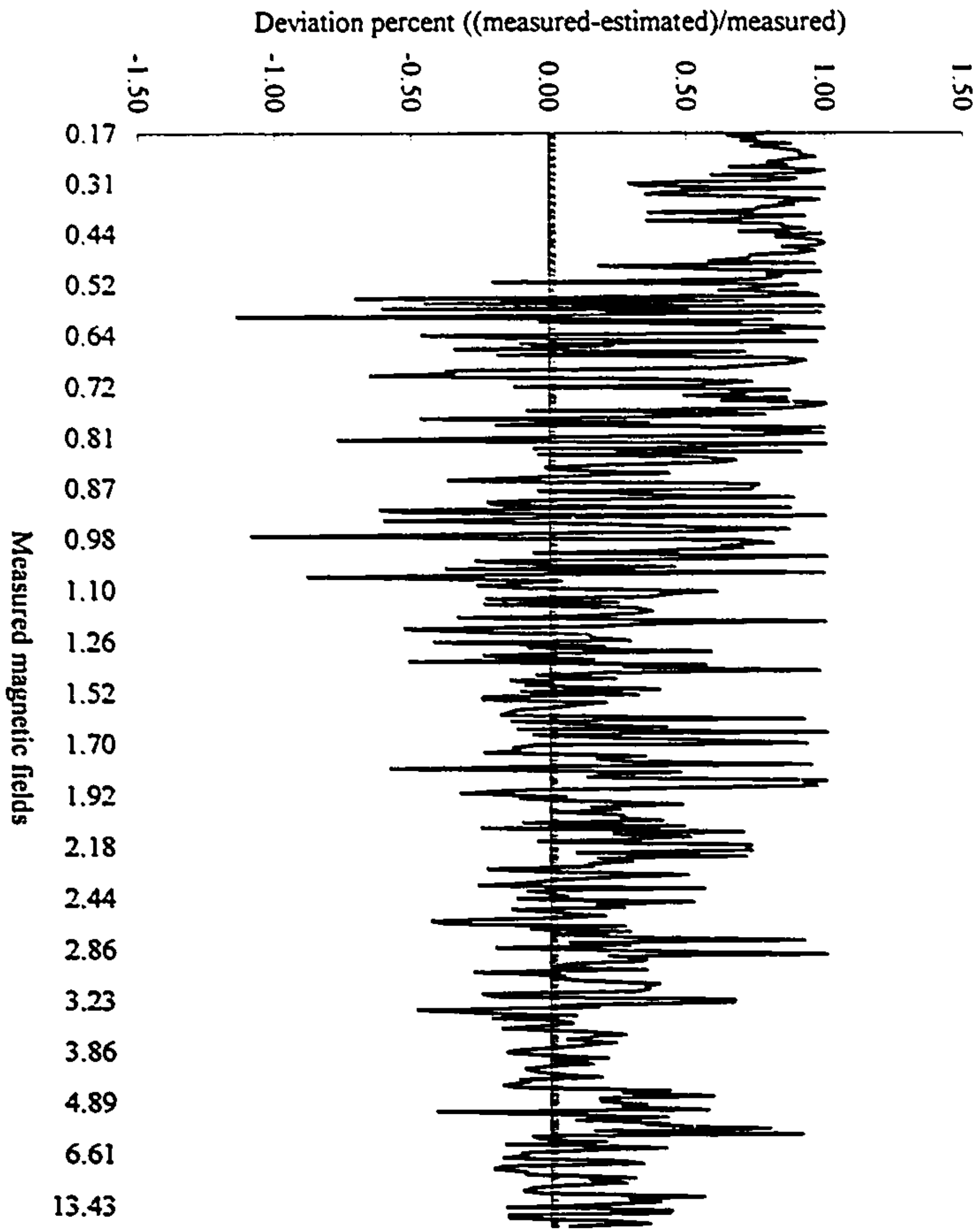
[c] the overall proportion of chance-expected agreement.

[d] weighted kappa

[e] standard error

[f] confidence interval

Figure 1.Deviation of estimated MF from measured MF



## CONCLUSION AND SUMMARY

One of the most significant changes that have occurred in our society over the past century is the development and use of electric power. Its increased generation and use have caused radical changes in human exposure to virtually the entire electromagnetic spectrum, including non-ionizing radiation such as radio-frequency signals (RF) and the extremely low frequency (ELF, 30-300 Hz) electric and magnetic fields associated with power generation, transmission, and substation systems. Considerable epidemiological studies have been carried out during the past 15 years to explore the potential biological interactions between the human body and power frequency (50 or 60 Hz) electric and magnetic fields. Even so, both the evidence concerning the carcinogenic effects of power frequency magnetic fields (MF) and the understanding of the mechanisms by which MF interact with living organisms are still limited. Questions as to the causal link between power frequency MF and human cancers are unanswered at this time.

This thesis appraised the epidemiological evidence from the studies of adult cancers in relation to residential exposure to MF. These studies have been less well reviewed than the studies of children and workers. The summarizing results from seven studies indicated an inconsistent association between MF and leukemia. Brain tumors and breast cancers, two other cancers which were frequently suspected of being associated with MF in the studies of children or workers, have rarely been investigated by the residential adult studies. Although the studies of children and workers are unable to provide convincing evidence causally linking MF with cancers at this time, they tend to consistently suggest a moderate association of MF with brain tumors, and a stronger association with leukemia.

This tendency should be carefully examined in future studies and should not be considered the mere play of chance. The only direct way to answer whether the results from residential adult studies would show the similar tendency as those from the studies of children and workers is to conduct additional studies with careful avoidance of methodological flaws.

The main contribution of this thesis was the results from three case-control studies with identical methodology and the same population base, which investigated the risk of leukemia, brain tumors, and female breast cancers, respectively. Adult leukemia was the only cancer under study to possess a significantly elevated risk (50%) from residential exposure to 60 Hz MF. These studies possessed several methodological strengths, including a large number of study subjects recruited in the studies of leukemia and female breast cancers, complete blindness during exposure assessment, and calculation of MF from presumably stable power information. Considering the identical methodology and population base of three case-control studies, the findings tend to strongly suggest a possible association between residential MF and adult leukemia. However, based sorely on the results of the present study, neither the causal relation between residential MF and leukemia nor the absence of the association of residential MF with brain tumors and female breast cancers can be confirmed at this stage. Nevertheless, given a very high statistical power for the study of female breast cancer, the findings may suggest that the causal relation, if any, between MF and female breast cancer should be very small.

The other integral part of this thesis was an analysis of the validity of MF estimated from power information of high-voltage power lines, a method which was occasionally used in previous epidemiological studies to assess residential MF, but was rarely validated empirically. Due to an incomplete consideration of all possible sources of indoor MF such as distribution lines and appliances, the MF estimated exclusively from transmission lines tended to underestimate the real MF actually measured by dosimeters. There appeared to be a tendency for the agreement between measured and estimated MFs to decline with the distance from the transmission lines. The agreement, based on the categorized MF with cutoff points of 1 mG and 2 mG, was estimated to be somewhere between 0.50 and 0.78 for a sample residences presumably representative of all residences in northern Taiwan with respect to the distribution of residential MF. The results suggested that using only power information of transmission lines to estimate residential MF may result in exposure misclassification.

Because the epidemiological study usually requires a large number of subjects to stabilize the fluctuation of risk estimates and a long period of time to obtain a stable MF exposure, it is very unlikely, if not impossible, to perform large-scale and long-term on site measurements of MF in epidemiological studies. It can be foreseen that surrogate methods like modeling power information will still be alternatively used to perform exposure assessment in future studies. From this perspective, the present study strongly suggested that more efforts should be devoted to further improve the accuracy of estimated MF by taking into account the other sources of MF. Meanwhile, a careful evaluation of validity of any surrogate method of MF exposure assessment which will be implemented in future epidemiological studies is also recommended.

The results from the present thesis do not unequivocally demonstrate that MF emitted from power lines causally increase cancer risks. However, given the methodological improvements this study does provide valuable epidemiological evidence for this important debate. In order to answer whether or not power frequency MF may contribute to increased cancer risks, it is important to conduct additional scientific studies that will reduce the uncertainty currently associated with the question of power lines and cancer.

APPENDIX: FORMULA FOR CALCULATING MAGNETIC FIELDS OF POWER LINES WITH SPECIFIED CURRENT

The ELF magnetic fields of a power line are related to electric currents on the line. For $N_c$ horizontal conductors, a simple formula that accounts also for the induced eddy currents in a conducting earth is

$$\overline{B} = -2\sum_{n=1}^{N_c} I_n \left\{ \left[ \frac{(y-d_n)}{r_{cn}^2} - \frac{(y+d_n+\alpha_g)}{r_{in}^2} \right] \overline{a}_x - \left[ \frac{(x-h_n)}{r_{cn}^2} - \frac{(x-h_n)}{r_{in}^2} \right] \overline{a}_y \right\}$$

mG (RMS)

$r_{cn} = \sqrt{(x-h_n)^2 + (y-d_n)^2}$, $r_{in} = \sqrt{(x-h_n)^2 + (y+d_n+\alpha_g)^2}$,

$\alpha_g = \sqrt{2}\delta_g e^{-j\pi/4}$, $\delta_g = 503\sqrt{\rho_g / f}$,

$\overline{a}_x$ and $\overline{a}_y$ are two vector units

$\rho_g$ is the earth resistivity ($\Omega$ m), $f$ is the frequency in Hertz, $I_n$ is the conductor current (amps-RMS), and all distances are in meters. The $n$ th conductor is located at $(h_n, d_n)$. Note that the earth current for each conductor is equal in magnitude and opposite in direction to the conductor current. In addition, each earth current is buried in the earth at a complex depth proportional to $\delta_g$, the skin depth of the earth.

In the computer program MAGFLD 2.0, nominal currents are specified for each phase conductor. In the deterministic case, the earth return current (assuming no neutral conductor) is automatically set equal to:

$$I_{earth} = -I_{ph} = -\sum_{n=1}^{N_p} I_n$$

where $N_p$ is the number of phase conductors, $I_{ph}$ is the vector sum of the currents on the phase conductors, and $I_{earth}$ is the earth return current (the above text was partially extracted from the publication by Olsen RG et al. *Development and validation of software for predicting ELF magnetic fields near power lines*, presented in the IEEE Power Engineering Society Summer Meeting, San Francisco, CA, 1994).

It is also noted that the above deterministic analysis was employed in this thesis to estimate residential 60 Hz magnetic fields, in which no current amplitudes variation and neutral conductor was considered.