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OCCUPATIONAL EXPOSURE TO POWER FREQUENCY MAGNETIC FIELDS AND RISK OF NON-HODGKIN'S LYMPHOMA

by

KAREN JOHNS

Thesis submitted to the
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ABSTRACT

Extremely low frequency magnetic fields (MF) have been associated with leukemia. The objective of this thesis was to determine the risk of non-Hodgkin's lymphoma (NHL) associated with occupational exposure to power frequency MF. We analyzed data collected through the Canadian National Enhanced Cancer Surveillance System (NECSS) from 1624 histologically confirmed incident cases of NHL and 1643 population controls. Every occupation held by subjects was categorized through blinded expert review according to its average MF exposure. Cumulative exposure indices were calculated for each subject. Adjusted odds ratios were calculated using logistic regression. We found no association between occupational exposure to MF and NHL risk. We did find an association between self-reported work with pesticides and NHL risk (OR 1.3, 95% CI: 1.0, 1.6). Our findings provide no support for the hypothesis that exposure to power frequency MF is a causal factor for NHL.

EXECUTIVE SUMMARY

Statement of the Problem: Extremely low frequency (ELF) electric and magnetic fields are produced in the generation, transmission, and use of electricity. Residential exposure to these magnetic fields has been associated with leukemia in children and occupational exposure to these magnetic fields has been associated with chronic lymphocytic leukemia in adults. Non-Hodgkin's lymphomas (NHL) are malignancies of lymphoid tissue and are closely related to the lymphoid leukemias. The incidence of NHL has been increasing over the past several decades, as has the use of electricity. The objective of this thesis was to determine if the risk of NHL and its various subtypes was associated with occupational exposure to ELF magnetic fields (MF) through a secondary analysis of data collected through the case-control component of the Canadian National Enhanced Cancer Surveillance System (NECSS).

Methods: We analyzed data collected from 1624 histologically confirmed incident cases of NHL and 1643 sex and age matched population controls. Occupational exposure to MF was assessed using: a) information provided by subjects in a mailed questionnaire on their lifetime occupational history including job title, duties, industry, and job start and end years for each occupation; and b) categorization of each occupation held by subjects according to its average MF exposure through blinded expert review. Form this information, cumulative exposure indices, along with other exposure indices, were calculated for each subject. Odds ratios were calculated using unconditional logistic regression. Adjustment was made for sex, 5-year age group, sex by 5-year age group, province, employment status, education, cigarette pack-years, work with pesticides, use of electric home heat as a primary method of home heating,

and occupational exposure to ionizing radiation. Conditional logistic regression models were also explored; results were similar to those of the unconditional model.

Results: We found no association between occupational exposure to MF and NHL risk, regardless of the exposure index used. The risks of NHL in subjects with low, medium, and high cumulative MF exposure relative to those with only background levels of exposure were 1.1 (95% CI: 0.8, 1.6), 0.8 (95% CI: 0.6, 1.1), and 0.9 (95% CI: 0.7, 1.3), respectively. Furthermore, we found no association between occupational exposure to MF and any particular subtype of NHL. We did find an association between self-reported work with pesticides and NHL risk (OR 1.3, 95% CI: 1.0, 1.6). We found no association between either smoking or occupational exposure to ionizing radiation and NHL.

Conclusions: Our findings provide no support for the hypothesis that power frequency MF exposure is a causal factor for NHL.

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LIST OF ACRONYMS

CI	confidence interval
CLL	chronic lymphocytic leukemia
EBV	Epstein-Barr virus
ELF	extremely low frequency
HIV	human immunodeficiency virus
HLTV-1	human T-lymphotrophic virus type 1
Hz	herz
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases ICD-9 (9th edition) ICD-10 (10th edition)
ICD-O	International Classification of Diseases-Oncology ICD-O/1 (Version 1) ICD-O/2 (Version 2) ICD-O/3 (Version 3)
MALT	mucosa-associated lymphoid tissue
MF	magnetic fields
NECSS	National Enhanced Cancer Surveillance System
NIEHS	National Institute of Environmental Health Sciences
NHL	non-Hodgkin's lymphoma
NOS	not otherwise specified
OR	odds ratio
REAL	Revised European-American Classification of Lymphoid Neoplasms
RR	relative risk
SEER	Surveillance, Epidemiology, and End Results
Sv	Sievert mSv milliSievert
T	tesla mT millitesla μT microtesla
V	volt kV kilivolt
WHO	World Health Organization

CHAPTER 1
INTRODUCTION

Extremely low frequency (ELF) electric and magnetic fields are produced in the generation, transmission, and use of electricity.[1] Thus virtually all people are exposed to these fields which have generally been assumed to be safe. However, in the 1970s the possible effects of these fields on health began to be questioned and investigated. In 1998, it was concluded by a working group for the National Institute of Environmental Health Sciences (NIEHS) that there was limited evidence that residential exposure to ELF magnetic fields (MF) is associated with the development of leukemia in children and that occupational exposure to ELF MF is associated with the development of chronic lymphocytic leukemia in adults.[2] The more recent International Agency for Research on Cancer (IARC) evaluation of static and ELF electric and magnetic fields concluded that there was "limited evidence in humans for the carcinogenicity of extremely low-frequency magnetic fields in relation to childhood leukemia" but inadequate evidence in relation to all other cancers.[3]

Non-Hodgkin's lymphomas (NHLs) are malignancies of the immune system that arise in lymphatic tissue. They are relatively common, affect all ages, and have been increasing in incidence over the past few decades. The NHLs are closely related to lymphoid leukemias, including chronic lymphocytic leukemia, a malignancy considered to be possibly associated with occupational ELF MF exposure. Both lymphoid leukemias and NHLs are cancers of the hematopoietic lymphoid system. The distinction between lymphoid leukemias and lymphomas is increasingly recognized to be largely artificial, reflected only in the pattern of spread in the individual patient rather than any basic

cellular or clinical differences.[4 (p. 13)] Thus we consider it plausible that the development of NHL may be associated with exposure to ELF MF.

The National Enhanced Cancer Surveillance System (NECSS) was a collaborative project between Health Canada and the Provincial Cancer Registries designed primarily to understand better the relationship between the environment and cancer. It includes a case-control component that consists of data for incident cases of 19 types of cancer and for population controls.

The research goal of this thesis is to determine the risk of developing NHL associated with exposure to power frequency (50-60 Hz) MF, a component of the ELF spectrum, using data from the case-control component of the NECSS. We will refer to these fields as MF without specifying the frequency when presenting and discussing the research results in this thesis document. In order to carry out this risk assessment, occupational exposure to MF was assessed for each subject based upon his or her complete occupational history and MF exposure assessments for each job in that occupational history. These job exposure assessments were performed by an expert in the electromagnetic radiation field without knowledge of case/control status. Covariates in the analysis included cigarette pack-years, employment status, education, work with pesticides or herbicides, use of electric heat as a primary method of home heating, and occupational exposure to ionizing radiation.

1.1 Research Objectives

Although the literature on the association between power frequency MF and NHL risk provides only weak support for such an association, the studies that have been carried out in this area to date have each had some limitations. In addition, the

literature in this area is limited. For these reasons, we decided to carry out our study to further knowledge in this area and to overcome some of the limitations in the studies conducted to date. The specific objectives of the thesis are:

1) to determine the risk of NHL associated with exposure to MF (specifically, power frequency MF); and
2) to determine the risk of the major histologic subtypes of NHL associated with exposure to MF.

1.2 Organization of the Thesis

In the thesis, a literature review follows this introductory chapter. Background information on NHL and MF, a brief review of known or suspected risk factors for NHL, a brief review of cancers suspected to be associated with MF exposure, and a review of the epidemiologic studies of occupational exposure to MF and NHL risk are included in the literature review chapter. The methods used in the research project are described in the next two chapters. Firstly, the methods used in the case-control component of the NECSS are described. Secondly, the methods used in this particular project are described, including the creation of the study population, MF exposure assessment of jobs, calculation of exposure indices, data management, and statistical analyses. These two chapters are followed by the results chapter where the results of the study are presented and the discussion chapter where the interpretation of these results, the strengths and limitations of the study, the limitations of all studies of occupational MF and NHL, and conclusions and recommendations are outlined.

CHAPTER 2
LITERATURE REVIEW

2.1 Background

Overview

Background information on both non-Hodgkin's lymphoma (NHL) and electromagnetic fields is provided in this section. In addition to providing general information on NHL, this section provides a review of the descriptive epidemiology of NHL, the classification schemes used to subdivide NHL, and the International Classification of Diseases-Oncology (ICD-O) system used in coding NHL cases. The descriptive epidemiology can be important in providing insights into etiology. The classification schemes are reviewed as it is well recognized that NHL is a group of heterogeneous malignances; thus it can be important in etiological research to subdivide them into more homogeneous groupings. Versions 1 and 2 of the ICD-O coding system are reviewed as both these systems were used to code the topography and histology of the cancer in the National Enhanced Cancer Surveillance System (NECCS) data used for our research project. This is followed by information on electromagnetic fields in general, and power frequency magnetic fields (MF), in particular.

2.1.1 Non-Hodgkin's Lymphoma

Lymphoid malignancies are neoplasms of the immune system where the cell of origin is one arising from the pluripotent hematopoietic stem cells committed to the lymphoid cell line. The lymphoid malignancies include lymphomas, lymphatic leukemias, and plasma cell neoplasms. If the proliferation of lymphoid cells takes place in the tissues, usually the lymph nodes, spleen and other lymphoid organs, and thus forms a

tumor mass, the malignancy is defined as a lymphoma. If the proliferation takes place mainly in the bone marrow and peripheral blood, the malignancy is defined as a lymphatic leukemia. It should be noted that there can be considerable overlap between lymphomas and leukemias.[5 (p. 388)] In fact, although in the past it was considered that lymphomas and leukemias are biologically and clinically distinct diseases,[6] the present consensus is if the lymphoid malignant cells are identical phenotypically and morphologically, leukemic or lymphomatous distribution of the malignancy represents different clinical presentations of the same disease. If the malignant cell has the morphology of plasma cells (which are terminally differentiated B-lymphocytes which produce antibodies), these malignancies are referred to as plasma cell tumors. They occur mainly in the bone marrow. Multiple myeloma is the most common plasma cell tumor.

Lymphomas are subdivided into Hodgkin's lymphomas and non-Hodgkin's lymphomas. Hodgkin's disease is distinguished from NHL by the presence of Reed-Sternberg cells on histological evaluation.[7] It is distinct from NHLs both in its descriptive epidemiolgy and its clinical features. The incidence curve for Hodgkin's disease is bimodal, with the first peak occurring between the ages 15 to 34 and the second between the ages 50 to 69.[8] Clinically, the spread of Hodgkin's disease is by contiguous lymphatic extension[6] (i.e., extension to adjacent regional lymph nodes). Hodgkin's disease can present as localized disease (and in these cases may require local radiation treatment only).[5 (p. 410)]

The remainder of the lymphomas are classified as NHLs. These are a group of heterogeneous diseases with variations of natural history, pathology, immunology, cytogenetics, and responses to therapy. The large majority are of B-cell origin. The

incidence of NHL increases exponentially with age. In most cases of NHL, the disease is widely disseminated at the time of diagnosis and systemic treatment is generally required. This is to be expected given that normal lymphoid cells circulate through the lymphatics and peripheral blood to distant lymphoid tissues.[9]

Most lymphomas arise in lymph nodes. Extra-nodal lymphomas arise in other components of the lymphoreticular system. This system includes, in addition to the lymph nodes, the spleen, thymus, and foci of lymphoid tissue within certain mucosal epithelia referred to as MALT (mucosa-associated lymphoid tissue). MALT includes lymphoid tissue in the oropharnyx and nasopharnyx (Waldeyer's ring: adenoids and tonsils), the gastrointestinal tract (Peyer's patches of the distal ileum, lymphoid aggragates in the colon and rectum) and the lung (bronchus-associated lymphoid tissue). In addition, NHLs occasionally arise in sites where no lymphoid tissue is known to exist, such as the skin and brain.[10] Extranodal presentation of NHL occurs in 15 to 25% of affected adult patients in the United States and up to 40 to 50% in Europe and the Far East.[11] The most common extranodal sites are the gastrointestinal tract and nasopharynx; other common sites include the brain, skin, bone, thyroid, breast, lung, and testis.[11]

Lymphomas often present with painless enlargement of one or more of the peripheral lymph nodes. If the lymphoma occurs in the internal lymph nodes or in an extranodal location such as the intestine, bone, or nasopharynx, it can present with symptoms due to its space occupying effects. Because of the generalized distribution of lymphoid tissue, practically any organ system can be affected by the occurrence of a lymphoma in or near it.[5 (p. 390)] In addition to the signs and symptoms due to local effects, lymphomas can result in generalized symptoms such as weight loss, fever,

profuse sweating, and severe itchiness. As tumors of the immune system, lymphomas can also lead to immune abnormalities resulting in increased susceptibility to infection and increased autoimmune manifestations.[9] While all lymphomas are considered malignant, some can be clinically indolent and compatible with survival for decades.[10] Paradoxically, clinically indolent, low-grade lymphomas are not curable, whereas approximately half of high-grade aggressive tumors, which can lead to death within months if not successfully treated, are curable.[5]

2.1.1.1 Classification of Non-Hodgkin's Lymphoma

The classification of hematopoietic and lymphoid neoplasms, especially NHL, has been confusing and controversial. This is due in part to the fact that the NHLs are a heterogeneous group of neoplasms and that knowledge regarding the immune system has been advancing fairly quickly. With the increased knowledge, older terms are no longer applicable and often incorrect. In addition, several different competing classification schemes with differing terminology have been used over the years and by differing groups in differing locations. The main purpose of many of the older classification schemes was to predict clinical behaviour in order to make treatment decisions.[10] These systems did not identify unique disease entities. Furthermore, problems with reproducibility of NHL classification have been well documented. In studies in both population-based and clinical settings, agreement among expert pathologists in classifying NHL cases according to the Working Formulation (one of the classification schemes in use since the 1980s) is only about 60%.[12] Ideally, a classification scheme for NHL should be scientifically accurate, reproducible by the average pathologist, and predict clinical behaviour while incorporating the presumed site of origin of the tumor, the presumed cell of origin, and the phenotype of the neoplastic

cell.[13] Commonly used classification systems in North America include the Working Formulation and the Revised European-American Classification of Lymphoid Neoplasms (REAL) system.[14] A new World Health Organization (WHO) classification of neoplastic diseases of the hematopoietic and lymphoid tissues was published in 2001.[15] The proponents of this classification system expect that it will become accepted internationally as the standard.[16] A more detailed description of these three classification schemes follows.

In the early 1980s at least six classification schemes were in current use. In 1982, the United States National Cancer Institute funded a study[17] to test these classification schemes. An international panel of hematopathologists examined 1,175 cases of lymphoma that had been prospectively staged and treated in a uniform manner at one of four major treatment centres (three in the United States, one in Italy.) The pathologists, after concluding that all six systems were of comparable usefulness, proposed 'A Working Formulation for the Non-Hodgkin's Lymphomas for Clinical Usage'[17] to allow translation of terminology from one system another. However, this formulation, presented in Table 2.1, became used as a major classification system in North America. In the Working Formulation, NHLs are classified by morphologic criteria into ten types designated with letters A through J. The morphologic criteria focus particularly on the pattern of tumor growth within lymph nodes (nodular or diffuse) and the size of the tumor cells,[9] in addition to the degree of cell differentiation and the presence of nuclear cleavage. These types are then grouped according to prognosis into low-, intermediate- and high-grade categories. The median survivals were approximately 6½, 2½, and 1½ years for each of these groups, respectively.[18] However, the survival curves overlap when followed for longer periods of time as patients in the low-grade group die from

Table 2.1. The Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage[17]

Prognostic group	Type	Median survival (years)
Low-grade	A. Small lymphocytic	5.8
Low-grade	B. Follicular, predominantly small cleaved cell	7.2
Low-grade	C. Follicular mixed, small cleaved and large cell	5.1
Intermediate-grade	D. Follicular, predominantly large cell	3.0
Intermediate-grade	E. Diffuse small cleaved cell	3.4
Intermediate-grade	F. Diffuse mixed, small and large cell	2.7
Intermediate-grade	G. Diffuse large cell	1.5
High-grade	H. Large cell, immunoblastic	1.3
High-grade	I. Lymphoblastic	2.0
High-grade	J. Small noncleaved cell; Burkitt's	0.7
Miscellaneous	Composite	
	Mycosis fungoides	
	Histiocytic	
	Extramedullary plasmacytoma	
	Unclassifiable	
	Other	

progressive lymphoma while those in the intermediate- and high-grade groups who were cured of their disease remain alive. This demonstrates the paradox of NHL management referred to earlier. It should be noted that the survival curves upon which these prognostic groups were initially based are not directly applicable to patients today because of improvements in treatment methods since 1982.[18] While the Working Formulation has been quite useful in making treatment decisions, it is less useful in increasing understanding of the etiology of NHL as it does not identify disease entities.

In 1994, the International Lymphoma Study Group (a group of 19 hematopathologists from United States, Europe, and Asia) developed, by a consensus approach, a classification of lymphoid malignances where the emphasis was on defining specific disease entities.[19] In this classification, referred to as the Revised European-American Classification of Lymphoid Neoplasms (REAL), lymphoid malignancies are divided into three major categories based upon their cell of origin: B-cell neoplasms, T/NK-cell neoplasms, and Hodgkin's disease. The B-cell and T/NK-cell neoplasm categories are further subdivided into precursor (lymphoblastic) neoplasms and peripheral (mature) neoplasms. Lymphomas, lymphoid leukemias, and plasma cell malignancies are included in this system. Each of the identified lymphoid malignancies is defined by a combination of morphologic, immunophenotypic, genetic, and clinical features and is simply listed in the appropriate stratum; each is believed to constitute a distinct clinicopathologic entity. The diseases, as listed by the International Lymphoma Group in the REAL, are presented in Table 2.2.

A new classification of hematological malignancies has recently been developed for the WHO by over 80 international hematopathology and clinical experts.[15] The previous WHO classification of leukemias and lymphomas was published in 1976 and is

Table 2.2. The Revised European-American Classification of Lymphoid Neoplasms[19]

B-Cell Neoplasms

I. Precursor B-cell neoplasm: Precursor B-lymphoblastic leukemia/lymphoma

II. Peripheral B-cell neoplasms
   1. B-cell chronic lymphocytic leukemia / prolymphocytic leukemia / small lymphocytic lymphoma
   2. Lymphoplasmacytoid lymphoma / immunocytoma
   3. Mantle cell lymphoma
   4. Follicle center lymphoma, follicular
   5. Marginal zone B-cell lymphoma
      Extranodal (MALT-type +/- monocytoid B cells)
   6. Provisional entity: Splenic marginal zone lymphoma
   7. Hairy cell leukemia
   8. Plasmacytoma / plasma cell myeloma
   9. Diffuse large B-cell lymphoma
   10. Burkitt's lymphoma
   11. Provisional entity: High-grade B-cell lymphoma, Burkitt-like

T-Cell and Putative NK-Cell Neoplasms

I. Precursor T-cell neoplasm: Precursor T-lymphoblastic lymphoma / leukemia

II. Peripheral T-cell and NK-cell neoplasms
   1. T-cell chronic lymphocytic leukemia / prolymphocytic leukemia
   2. Large granular lymphocyte leukemia (LGL)
   3. Mycosis fungoides / Sezary syndrome
   4. Peripheral T-cell lymphomas, unspecified
   5. Angioimmunoblastic T-cell lymphoma
   6. Angiocentric lymphoma
   7. Intestinal T-cell lymphoma
   8. Adult T-cell lymphoma / leukemia
   9. Anaplastic large cell lymphoma
   10. Anaplastic large cell lymphoma, Hodgkin's-like

Hodgkin's Disease

I. Lymphocyte predominance

II. Nodular sclerosis

III. Mixed cellularity

IV. Lymphocyte depletion

V. Provisional entity: Lymphocyte-rich classical Hodgkin's disease

now outdated. In the new WHO classification, hematological malignancies are stratified according to their lineage into myeloid neoplasms, lymphoid neoplasms, mast cell disorders, and histiocytic neoplasms. The classification of lymphoid malignancies is based upon the REAL system, but some revisions have been made in light of new data available since 1994 for some categories of lymphoma and leukemia.[20] This classification represents the first worldwide consensus on the classification of hematologic malignant neoplasms. It is anticipated that use of this classification will facilitate research in the etiology of this heterogeneous group of malignancies by identifying distinct biological entities and by allowing the use of common terminology between research groups.[16]

2.1.1.2 Descriptive Epidemiology

Non-Hodgkin's lymphoma is, as of 2000, the fifth most commonly occurring neoplasm in both Canada[21] and the United States[12] (after cancers of the breast, prostate, lung, and colon). It can occur at any age, and is one of the more common childhood cancers. However, it occurs more commonly in adults. The incidence increases steadily with age, although certain types are more likely to occur in specific age groups. The average age at diagnosis is 45 to 55 years and the median age is 60 to 65 years.[11] NHL occurs more often in males than females; incidence is approximately 40% higher in men than in women.[11] In the United States, it occurs more frequently in whites than in Americans of African, Japanese, or Chinese descent.[14] The five-year relative survival rate is about 50% in both sexes.[22]

Non-Hodgkin's lymphoma has been described as an emerging epidemic because, worldwide, incidence and mortality have been rising rapidly.[23] This trend of increasing

NHL rates has been evident in the United States and Scandinavian countries since the 1950s.

Analyses by Rabkin *et al*[24] of data from the Surveillance, Epidemiology, and End Results (SEER) program (a program which collects data from nine population-based cancer registries in the United States) demonstrated that the incidence rates for NHL increased exponentially with age between 20 and 79 years and that these rates were higher for males than females. The incidence rates for the period 1984-88 varied from 2.3 to 86 per 100,000 in males and from 1.5 to 68 per 100,000 for females. For four of the SEER areas (Atlanta, Detroit, San Francisco, and Connecticut), incidence data were available from the 1940s. From the period 1947-50 to the period 1984-88, annual NHL incidence among whites increased 150%. The age-adjusted (1970 US standard) incidence rates for those periods increased from 6.9 to 17.4 per 100,000 in men and from 4.7 to 11.6 per 100,000 in women, with a consistently increasing trend noted throughout. Mortality increased more slowly than incidence, although the pattern was the same. Between 1950-54 and 1985-88 mortality increased by 90% among whites, from 4.0 to 7.4 per 100,00 among men and from 2.6 to 5.0 per 100,000 among women. The investigators noted that the increases in NHL were not uniform for all age groups, or for histological types or sites of NHL. The changes in incidence were greater in the older age groups and in the 1980's NHL increased abruptly in men aged 25 to 54 due to lymphomas associated with the AIDS epidemic. The changes in incidence were also greater for those NHLs with high-grade histology, as classified by the Working Formulation. Between 1978 and 1988, high-grade NHL increased nearly 15% per year compared with low-grade which increased 3% per year, although the largest absolute increase was noted in diffuse large cell (an intermediate-grade lymphoma). Extranodal

disease increased more rapidly than nodal disease, with race- and sex-specific increases of 3.0 to 6.9% for extranodal cases compared with 1.7 to 2.5% per year for nodal disease.

The earliest NHL incidence data available are from 1935. An analysis based upon all NHL cases reported to the Connecticut Tumor Registry between 1935 and 1988 showed that there has been an increase in the rates since 1935, with a 10.3% increase in risk for females and 9.2% for males every 5 years since 1965. Reporting of cancer cases to this registry was thought to be essentially complete since 1965.[25]

In Canada the age-standardized incidence rates for NHL, as reported by the National Cancer Institute of Canada, have nearly doubled from 1974 to 1998. These rates, which are based on the age distribution of the 1991 Canadian population, increased from 10.1 per 100,000 in 1974 to 19.3 in 1998 in males, and from 8.1 per 100,000 in 1974 to 13.9 per 100,000 in 1998 in females.[21]

In addition, data published in the early 1990s from 20 registries from countries throughout the world (including India, Japan, Columbia, Brazil, Singapore, and Puerto Rico) have indicated an increasing incidence of NHL from around 1970 to 1980 or 1985.[24 26 27 28]

The reasons for the increase in NHL rates have not been determined. Risk factors for NHL have been identified, but none that can account for more than a minor portion of the trend. In fact, Hartge and Devesa[29] estimated that, after accounting for the likely effects of misdiagnosis of Hodgkin's disease as NHL, the inclusion of new entities, familial factors, human immundeficiency virus (HIV) infection and other immunosuppressive conditions or drugs, and occupation, 80% of the increased incidence of NHL in the United States from 1947-50 to 1984-88 in all males and 42%

among males aged 0 to 64 remains unexplained. They noted that an agent carrying a relative risk of 2 would have to rise in prevalence from 0 to 80% to produce the increased incidence observed in all males and from 0 to 42% to produce the increase observed in men under the age of 65.

It is possible that some of the apparent increase in incidence could be attributed to artifactual factors including completeness of registration, changes in disease classification, and advances in diagnostic technology. However, the increased rates in the Connecticut incidence data have been reviewed taking into account these factors and also changes in related diseases such as AIDS with the conclusion that the increased rates are real and cannot be totally accounted for by these factors alone.[25] In addition, others have reached similar conclusions.[30 31]

Incidence rates also vary considerably by geography. Age-standardized incidence rates (standardized to the world population) reported in 2001 varied from approximately 2 to 3 per 100,000 in Thailand and China to 14 per 100,000 in the United States.[28] Incidence rates in Canada and the United States are among the highest in the world. In Canada, incidence rates for NHL appear to vary by province. It is reported in the Canadian Cancer Incidence Atlas that incidence rates of NHL for the time period 1986-90 were higher in Manitoba for both sexes, in Saskatchewan for females, and in Ontario for females, while the rates in Alberta, Newfoundland, Nova Scotia, and Prince Edward Island were generally lower for both sexes.[22] Geographic clustering of certain subtypes of NHL is also reported: the endemic form of Burkitt's lymphoma in children in central Africa; adult T-cell leukemia/lymphoma in southwestern Japan and the Caribbean; and small intestinal lymphoma with associated immunoglobulin disorders in the Middle East.[18]

2.1.1.3 Coding of Non-Hodgkin's Lymphoma Using the ICD-O

Disease entities are often assigned codes for the purposes of creating and maintaining databases and statistics for surveillance and statistical analyses. The most commonly used system for coding diseases is the International Classification of Diseases (ICD), of which the 10th edition (i.e., ICD-10) is the most current. In order to provide greater detail in coding cancers than that provided by the ICD, the International Classification of Diseases-Oncology (ICD-O) is often used.

The ICD-O is a coded nomenclature for neoplasms which provides for coding of both topography (site of origin) and morphology (including histology, behaviour, and grading) of tumors. It does not provide codes for stage or extent of disease. Further, despite its title, it is in fact "not a classification scheme for neoplasms", and often contains terms for neoplasms from more than one classification scheme.[32 (p. xxiv)] The ICD, upon which the topography section of ICD-O is based, provides codes for tumors that take into account topography and behaviour (benign, malignant, etc.) but not histology. Three versions of the ICD-O have been published to date; the particular version is indicated by the digit following the slash in the acronym (i.e., ICD-O/1 refers to Version 1, ICD-O/2 to Version 2, and ICD-O/3 to Version 3). The first version was published in 1976, the second in 1990, and the third in 2000. Details regarding the first two versions but not the third are provided below because codes from the first two versions were used in the coding of NHL cases included in our research project.

Topography codes: The topography codes in ICD-O/2 (i.e., Version 2) are four character alphanumeric codes running from C00.0 through C80.9. These codes are based on the ICD-10 in which an alphanumeric system is used. The first character of ICD-10 codes is a letter; the letter C is assigned to all malignant neoplasms. The

decimal point indicates subdivisions of the three-character rubric or category. For example, in ICD-10 the category C77 is used for secondary and unspecified malignant neoplasms of the lymph nodes; in ICD-O/2 the topography rubric C77 contains the topography codes used for lymph nodes: C77.1 is the ICD-O/2 code for 'intrathoracic lymph nodes', C77.8 is the code for 'lymph nodes of multiple regions', and C77.9 is the code for 'lymph node, NOS (not otherwise specified)'. For a further example, while the C42 category is vacant in ICD-10, it is used to designate several topographic sites within the hematopoietic and reticuloendothelial systems in the ICD-O/2. Specific codes within this category include C42.0 for 'blood', C42.1 for 'bone marrow', C42.2 for 'spleen', and C42.2 for 'reticuloendothelial system, NOS'. In coding the topography of a tumor using the ICD-O/2, most lymphomas occurring in lymph nodes are coded to the C77 category while most leukemias and related conditions are coded to the C42 category.[4 (p. 7)] Extranodal lymphomas are coded to the site of origin, for example the code C16.2 is used for a lymphoma originating in the body of the stomach; if the site of origin is unknown but is suspected to be extranodal, the code C80.9 for 'unknown primary' is used.[4 (p. 26)]

The topography codes in ICD-O/1 (i.e., Version 1) are based on the four digit numeric codes from Chapter II of ICD-9 and run from 140.0 to 199.9. The decimal point indicates subdivisions of the three digit rubrics. Lymph nodes fall in the topography rubric 196 with 196.8 coding for 'lymph nodes of multiple regions'. The topography rubric 169 includes codes for sites in the hematopoietic and reticuloendothelial systems; 169.0 for 'blood', 169.1 for 'bone marrow', 169.2 for 'spleen', 169.3 for 'reticuloendothelial system, NOS', and 169.9 for 'hematopoietic system, NOS'. The ICD-9 codes ranging from 200 to 208, which are used to code for

malignant neoplasms of lymphatic and hematopoietic tissue such as reticulosarcoma, lymphosarcoma, Burkitt's lymphoma, and mycoses fungoides in the ICD-9, are not included as topography codes in the ICD-O/1. These 200-208 codes are not necessary in the ICD-O "because the neoplasms coded to these rubrics are completely characterized by the morphology code numbers in ICD-O combined with appropriate topography code numbers." [33] (p. vii)

Morphology codes: The morphology codes in the ICD-O are six digit numbers, with a slash after the first four. These codes are used to describe the histology, behaviour, and grade of a neoplasm. The first five digits run from 8000/0 to 9989/1. The first four digits indicate the specific histologic classification. The first number following the slash (i.e., the fifth digit) indicates the behaviour. The behaviour codes are as follows: 0 'benign'; 1 'uncertain whether benign or malignant'; 2 'carcinoma in situ'; 3 'malignant, primary site'; 6 'malignant, secondary site'; and 9 'uncertain whether primary or metastatic'. The second number following the slash (i.e., the sixth digit) generally indicates the grade or differentiation of the neoplasm. In the case of leukemias and lymphomas, it is used to identify T- or B-cell origin and is coded as 5 for 'T-cell', 6 for 'B-cell', 7 for 'null cell', and 9 for 'cell type not determined'. As an example, the ICD-O morphology code for 'malignant lymphoma, large cell, diffuse, NOS (not otherwise specified)' of B-cell origin is 9680/36.

The NHL morphology codes for the lymphoma section of the second version of the ICD-O was remodeled from the first. New codes were introduced and older codes were dropped. The ICD-O/2 provides morphology terms for all major classification schemes for lymphomas that were use at the time of its revisions, and includes entities recognized in the Working Formulation. The ICD-O/1 includes terms, which are

generally not used now, from the original 1976 WHO classification[34] in which NHLs are divided into lymphosarcomas and reticulosarcomas.[32 (p. xxxii)]

2.1.2 Electromagnetic Fields

Weak electric and magnetic fields are produced by the generation, transmission, and use of electrical energy.[1] The electric fields arise from the presence of electric charge and are a function of voltage. The magnetic fields (MF) arise from the movement of the charge and are a function of current. The electric power used in homes, offices, and factories uses alternating current (AC). Batteries produce direct current (DC). Direct current flows steadily in one direction, while alternating current alternates direction, 60 times per second (60 Hz) in North America and 50 times per second (50 Hz) in Europe. For alternating current, the fields oscillate with the current.[35] These alternating fields are part of the electromagnetic spectrum, which also includes x-rays, ultra-violet light, visible light, microwaves, and radiofrequency energy. The components of the spectrum are defined by the frequency of the alternating fields. Power frequency electromagnetic fields are classified as extremely low frequency (ELF). Extremely low frequency includes frequencies of greater than 0 up to 3000 Hz.[36]

In general, electromagnetic sources produce both radiant energy (i.e., radiation) and non-radiant fields. Radiation propagates away from the source as electromagnetic waves, in which the electric and magnetic fields are tightly coupled. The frequency and wavelength of these waves are related such that their product is equal to the speed of light. These waves exist only in the 'far field', which generally begins at approximately one wavelength from the source. The non-radiant electric and magnetic fields exist near the electromagnetic source and are not projected into space. These fields occur in

the 'near field', where the distance from the source is shorter than the wavelength of the electromagnetic radiation. In the near field, the electric and magnetic fields can be considered as independent entities. In the case of ELF electromagnetic radiation, the wavelengths are in the range of thousands of kilometers (e.g., 5000 km for 60 Hz). Thus, while ELF electromagnetic sources, such as powerlines, transformers, appliances, and other electrical equipment, theoretically radiate some energy, the amounts are minimal. Human exposure generally occurs at distances from the source that are much shorter than the wavelength of the radiation, i.e., where near field conditions prevail. As such, the electric and magnetic fields of ELF electromagnetic sources are treated as separate entities using the so-called 'quasi static' approximation and the radiation component is ignored.[3 36 37]

Magnetic fields move easily through most materials, including buildings and tissue, while electric fields are blocked by intervening grounded objects that conduct electricity and are significantly attenuated by tissue.[38] This is one of the reasons why research has focused on MF effects.[37] Magnetic field exposures are most intense where high current exists, for example, occupational exposure to arc welding or induction heating and residential exposure to electrical appliances.[38] The intensity of these fields falls sharply with distance from the source.[39] Because MF are produced by either the movement of electric charges (i.e., the flow of current) or by permanent magnets, the MF produced by electrical equipment are present only when this equipment is turned on. In contrast, electric fields, which are produced by voltage, are present when the equipment is connected to the source of power, regardless of whether it is switched on or off.[40]

Magnetic field strength is usually quantitated by the magnetic flux density (denoted by the symbol B) measured in Tesla (T) in the Systeme International (SI). In the older centimeter-gram-second (CGS) system, magnetic flux density is measured in gauss (G), where 10,000 G equals 1 T or equivalently, 1 G equals 100 μT. In the epidemiologic literature, MF strengths are generally reported in units of either μT or mG; 0.1 μT equals 1 mG. Electric field strength is measured in units of volts/meter (V/m).

Exposure to ELF electromagnetic fields is ubiquitous, with most exposure in the general population coming from electrical appliances, household wiring, and AC transmission and distribution lines.[41] In the occupational setting, there is the potential for larger and more varied exposures. Workers may be exposed to higher MF if they work near electrical systems that use large amounts of electric power (e.g., large electric motors, generators, or the power supply of electrical cables of a building). The strength of the MF depends on equipment design and current flow, as well as on the distance of the worker to the source. In general, MF exposures are poorly correlated with exposure to electrical fields.[42]

2.1.2.1 Typical Magnetic Field Strengths

The earth produces a static magnetic field, the strength of which varies from 30 to 70 μT. Natural phenomena, such as thunderstorms and solar activity, produce time-varying MF with frequencies in the power frequency range, usually of low strength, approximately 0.01 μT. However, during intense magnetic storms (i.e., fluctuations in the earth's magnetic field resulting from solar activity), these fields can reach intensities of 0.5 μT.[39]

In residences and office environments, the average power frequency MF are between 0.1 and 0.3 μT.[41] The distribution of background MF as measured over 24

hours or longer in studies done in the United States had a geometric mean of 0.06 to 0.07 μT and an arithmetic mean of 0.11 μT.[43] Background fields are generally lower in the United Kingdom and Europe. Household appliances produce MF, some on the order of 50-150 μT,[41] but these fields decrease rapidly with increased distance from the source, as a function of between the inverse square and inverse cube of the distance.[3] (Magnetic field strengths decrease more rapidly with distance from point sources such as appliances than from line sources such as powerlines.)[44] Appliances with high-speed electric motors or heating elements, such as microwave ovens, electric washing machines, dishwashers, or can openers produce the highest MF; these appliances can have MF greater than 0.2 μT at 1 meter.[42] Electric blankets have been associated with MF exposures to users of 0.25 μT in Australia.[39] In a survey of 1,000 people in the United States, the geometric mean 24-hour personal MF exposure was 0.09 μT; 14% of the population had exposures above 0.2 μT, and 2.5% above 0.5 μT. Personal exposures within the home averaged 0.8 μT for time not in bed, and 0.05 μT for time spent in bed, and at work averaged to 0.1 μT.[1 (p. 11)] These personal measurements are expected to be higher than measurements of background fields because they include exposures from sources such as appliances.[3 (p. 57)]

Higher exposures can occur in the occupational setting. Industrial processes using large magnets, induction motors, or heating devices can produce intense MF. For instance, MF of 8 to 70 mT (i.e., 8,000 to 70,000 μT) have been documented in the steel industry in Sweden.[39] Around power generating stations, average fields may be as high as 40 μT, and peak fields of 270 μT may be encountered.[41] Exposures as high as 130 mT (130,000 μT) peak fields can be experienced by arc welders,[41 45] with a geometric mean exposure of 4.1 μT for these workers reported in one study.[46] In arc

welders, the welding cable, which carries very high current until the arc is struck, is at most an arm's length from the body. Magnetic field strengths ranging from 0.32 to 11.1 μT are present near industrial sewing machines, with average exposure during a full shift measured from 0.21 to 3.20 μT.[3 (p. 66)] In a study in which 20 electric utility workers wore personal exposure meters for one week, the geometric mean of the time-weighted average MF exposure was 1.7 μT for work periods, 0.31 μT for non-work periods and 0.16 μT for sleep.[47] In a larger study of work sites of workers considered electrical workers in early epidemiologic studies (e.g., electricians, power line workers, welders, radio, and TV repairers), the geometric mean of spot measurements of MF was 0.50 μT, and at residences was 0.06 μT.[46]

Underneath overhead transmission lines, the average MF strength can reach 30 μT for multiconductor 765 kV lines and 10 μT for 380 kV lines.[41] These fields generally fall to background levels at distances of 50 to 300 meters from these high voltage lines.[3 (p. 59)] At ten meters from a 12 kV distribution line, MF range from 0.2 to 1.0 μT.[36] Because the voltages of power lines are closely regulated, the electric fields produced by these transmission lines are fairly constant whereas the MF can vary from day-to-day, and within the day, depending upon power usage and thus current load.[36]

2.2 Risk Factors for Non-Hodgkin's Lymphoma

The etiology of non-Hodgkin's lymphoma (NHL) is largely unknown and in the majority of cases occurs in people with no known risk factors.[48] However, there are some well-established risk factors for NHL. These include: factors associated with immune dysfunction, particularly immunodeficiency but also autoimmune diseases; certain infectious agents; and certain demographic factors. Other potential risk factors

for NHL that have been studied include: physical and chemical agents, such as pesticides, benzene and other organic solvents, hair dyes, chemotherapy, and ionizing and ultraviolet radiation; lifestyle factors such as socioeconomic status, occupation, diet, smoking, and alcohol intake; and medical history factors such as infections, blood transfusions, vaccinations, and allergy. Only the established risk factors and the potential risk factors of interest to us in regard to our research are reviewed below. This review is based, in part, on recent reviews completed by Armitage *et al*[14] in DeVita's textbook on oncology, Melbye and Trichopoulos[28] in the Adami text on cancer epidemiology, Scherr and Mueller[49] in the Schottenfeld cancer epidemiology text, and Groves *et al*[12] in a journal article.

2.2.1 Immunodeficiency

It is well established that immunodeficiency is associated with an increased risk of NHL. This effect may be due to chronic antigenic stimulation as a result of an increased predisposition to infections; the lack of immune surveillance of damaged cells; or facilitation of viral replication in the immunosuppressed individual. The Epstein-Barr virus (EBV), the virus which causes infectious mononucleosis by infecting B-lymphocytes, is often associated with lymphomas that occur in the setting of immunosuppression.

2.2.1.1 Congenital Immunodeficiencies

A marked increased in the occurrence of lymphoproliferative disorders, including NHL, has been demonstrated in children with several of the rare inherited diseases characterized by immunodeficiency.[50] These diseases include the autosomal recessive multisystem disorder ataxia-telangectasia in which the relative risk of lymphoma is more

than 250;[51] the X-linked Wiskott-Aldridge syndrome in which the relative risk of malignancy (NHL accounts for the majority of the malignancies) is greater than 100;[52] common variable immunodeficiency and severe combined immunodeficiency, in which the relative risk of lymphoma is around 30 in both; and the X-linked lymphoproliferative syndrome in which the relative risk is 200.[52] The lymphomas occurring in association with these diseases are often extranodal and of high-grade histology. They generally occur during childhood, the exception being those associated with common variable immunodeficiency, which occur in adulthood, most frequently between the ages of 40 to 69.[53] The EBV appears to be an important cofactor in the development of these lymphomas.[50]

2.2.1.2 Acquired Immunodeficiencies

Human Immunodeficiency Virus: It is well established that the incidence of NHL in individuals with human immunodeficiency virus (HIV) infection is increased and that a portion of the noted increased incidence can be attributed to the AIDS epidemic which began in 1981. Patients with acquired immunodeficiency secondary to HIV infection are at approximately 60- to over 100-fold risk of NHL.[54 55] For instance, in a study based on linking AIDS and cancer registries in selected areas of the United States, an increased risk of NHL (RR 165) for people in the first 3.5 years after an AIDS-defining diagnosis other than NHL compared with people without AIDS was reported.[56] In another study, it was reported that nearly 30% of HIV-infected individuals receiving anti-retroviral therapy developed NHL within 36 months.[57] The risk of NHL occurrence in HIV-infected individuals appears to increase with decreasing immune function as measured by CD4+ lymphocyte counts.[28] The introduction of highly active antiretroviral therapy (HAART) in late 1996 resulted in improvement in immunocompetence in HIV-

infected patients with an apparent decreased incidence of NHL.[58] In a study of cancer incidence in HIV-positive individuals in developed countries, adjusted incidence rates (expressed as cases per 1,000 person-years) for NHL declined from 6.2 in the time period 1992-96 to 3.6 in 1997-99.[59] The lymphomas associated with AIDS are predominantly extranodal tumors of B-cell origin with high-grade histology, and primary lymphoma of the brain is not uncommon. Nearly all of the primary central nervous system lymphomas[60] and approximately half of the remainder of the lymphomas associated with HIV are EBV-genome positive.[49]

Post-transplantation immunosuppression: The risk of developing lymphoproliferative disorders, including NHL, following solid organ transplantation or allogenic bone marrow transplantation is increased, and the lymphomas are nearly always associated with EBV.[14] This risk appears to be greater in patients who receive more aggressive immunosuppression and in patients who receive heart and liver transplants compared to those who receive kidney transplants. In addition to the level of immunosuppressive therapy, the level of antigenic stimulation of the immune system by the implanted graft may be related to the increased level of risk.[28] In a follow-up study of 3,834 renal transplant patients in the UK and Australia from 1970 through to 1978, 34 cases of NHL were diagnosed, 19 within 2 years of transplant, with the overall risk calculated as 60 times that in the general population.[61] In a more recent follow-up study of a series of 45,141 kidney and 7,634 heart recipients, the incidence of NHL in the first year following transplant was 0.2% and 1.2% (about 20 and 120 times higher than the incidence in the general population), respectively; the incidence rates were lower in subsequent years. The risks were greater in patients who received more aggressive immunosuppressive regimens.[62] In a 1999 study, the cumulative incidence

of lymphoproliferative disorders at ten years after bone marrow transplantation was reported to be 1.0% +/- 0.3%, with the majority (64/78) occurring less than one year after transplantation.[63]

2.2.2 Autoimmune Disorders

An increased risk of NHL has been reported for a number of different autoimmune disorders including rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, celiac disease, and dematits herpetiformis.[28] For example, patients with Hashimoto's thyroiditis and Sjogren's syndrome are predisposed to developing NHL involving the thyroid and lacrimal or salivary glands, respectively.[64] Although the increased risk may be due to treatment of these disorders with chronic immunosuppressive therapy, increased risk has been observed among patients with these conditions not treated with immunosuppressive therapy.[64] For instance, increased risks have been reported in patients with rheumatoid arthritis (RR 2.5) or Sjogren's syndrome (RR 36.0) who did not receive any immunosuppressive therapy.[65] Further, in a nested case-control study within a cohort of patients admitted to hospital with rheumatoid arthritis in Sweden, high inflammatory activity was associated with an increased risk of NHL compared to those with low inflammatory activity (OR 25.8, 95% CI: 31, 213). This risk persisted after adjustment for drug treatment.[66]

2.2.3 Infectious Agents

There are several infectious agents that have been associated with the development of NHL. One of the more important is HIV, which has been reviewed above under acquired immunosuppression. The human T-lymphotrophic virus type 1

(HTLV-1) is considered the causative agent of adult T-cell leukemia/lymphoma. In addition, several other infectious agents have been associated with lymphomas, including: Helicobacter pylori in gastric lymphomas; human herpersvirus 8 in primary effusion lymphoma; and EBV and possibly hepatitis C virus in some B-cell lymphomas.[28] Human T-lymphotrophic virus type 1, Helicobacter pylori, and EBV are reviewed below.

2.2.3.1 Human T-Lymphotrophic Virus Type 1

Human T-lymphotrophic virus type 1 is a human type C retrovirus that is endemic in southwestern Japan, the Caribbean, and parts of Central Africa and South America.[11] The virus was first isolated from a patient with cutaneous T-cell lymphoma in 1980 and is considered a causative agent of adult T-cell leukemia/lymphoma as well as of HTLV-1 associated myelopathy/tropical spastic paraparesis.[67] The latent period between infection and development of the T-cell leukemia/lymphoma is several decades;[68] the risk of developing disease is up to 5% in infected patients,[67 69] and is highest in those who are infected early in life.[70]

2.2.3.2 Helicobacter pylori

Helicobacter pylori is a gram negative bacteria that causes a chronic infection of the stomach. It is implicated in the pathogenesis of gastric mucosa-associated lymphoid tissue (MALT) lymphomas. It is often found in the gastric mucosa of patients with these lymphomas and patients with gastric lymphomas are more likely than controls to have serologic evidence of past infection.[14] For instance, in an American nested case-control study in which serum samples had been taken on average 14 years before diagnosis, gastric lymphoma was associated with evidence of previous infection (OR 6.3, 96% CI: 2.0, 19.9).[71] Further, eradication of Helicobacter pylori infection in the early stage of gastric MALT lymphomas has been reported to result in tumor regression.[72]

2.2.3.3 Epstein-Barr Virus

The Epstein-Barr virus is a DNA herpes virus that infects B-lymphocytes and is the causative agent of infectious mononucleosis. It is a ubiquitous infection and appears to play an important role in the B-cell lymphomas associated with immunodeficiency. The virus was first discovered in cell lines from tumors of patients with African (endemic) Burkitt's lymphoma.[14] It is associated with over 95% of endemic Burkitt's lymphomas (in which malaria is a cofactor) and less commonly with sporadic Burkitt's lymphoma.[73] The NHLs associated with transplantation are nearly all EBV positive, while many but not all of those associated with the congenital immune deficiencies or with HIV infection are EBV positive.[74] Epstein-Barr virus causes proliferation of the infected B-lymphocytes, which is normally suppressed by host immune responses mediated by T-lymphocytes. Thus, a mechanism of lymphoma development associated with EBV may be the uncontrolled proliferation of clones of these EBV-transformed B-cells in patients with depressed T-cell mediated immunity.[14] In addition, as suggested by the association of EBV and malaria in endemic Burkitt's lymphoma, lymphoma development may result from the transforming effects of EBV coupled with the effects of chronic immunological stimulation due to malaria [5 (p. 417)] or other factors such as organ transplantation or other infections.

2.2.4 Genetic and Demographic Factors

As noted in section 2.1.1.2 in which the descriptive epidemiology of NHL was discussed, the incidence of NHL increases steadily with age, although certain types are more likely to occur in specific age groups. It is more common in males than females; and is more common in whites than blacks. As speculated by Melbye and Trichopulos, it

is possible that the decreased incidence in females is due to some role of hormones in the development of lymphoma.[28]

Chromosomal translocations and trisomy 12 have been associated with particular types of NHL.[12] Cytogenetic abnormalities can be identified in more than 85% of NHL specimens and specific abnormalities correlate with histology and immunophenotype. The most common abnormalities are translocations involving antigen receptor genes.[73]

Familial aggregation of NHL has been described with a 3- to 4-fold increased risk in close relatives of patients with lymphomas or other hematopoietic neoplasms.[11] (p. 2453) This risk may reflect genetic factors and/or gene-environment interactions.[12]

2.2.5 Social and Behavioural Factors

2.2.5.1 Socioeconomic Status

In ecological analyses, mortality rates for NHL generally increase with socioeconomic status level. For example, in a study from the United States reported in Schottenfeld's text, mortality rates were found to be higher in countries with higher median educational levels among residents. Counties were ranked by the median educational level of residents as an indicator of socioeconomic status. The age-adjusted mortality rates of NHL from 1950 to 1969 for the counties in the upper 10% of the distribution for median educational level were compared to those in the lower 10%; the ratios obtained for these comparisons were 1.4 for males and 1.5 for females.[49] (p. 925) International data also tend to follow this pattern with higher incidence rates in countries with increased level of economic development.[28 49] However, studies based on individuals that were also reported in Schottenfeld's text do not confirm these findings. In a case-control study in Italy, the risk of NHL was lower in subjects with 12 or more

years of education compared to those with fewer than 7 years (OR 0.6, 95% CI: 0.4, 1.0). In the Third National Cancer Survey, no consistent pattern between socioeconomic status and incidence rates of NHL was observed.[49 (p. 925)]

2.2.5.2 Occupation

While there have been no consistent reports of an association of occupation with NHL risk, excess risks have been reported for farmers, pesticide applicators, grain millers, wood and forestry workers, chemists, cosmetologists, machinists, printers, and workers in the petroleum, rubber, plastic, and synthetic industries.[28] In a meta-analysis of 36 studies, the combined relative risk for farmers was 1.1 (95% CI: 1.0-1.2) although significant heterogeneity was detected for study design and country.[75]

2.2.5.3 Cigarette Smoking

Smoking has been considered as a risk factor for NHL but the results of epidemiologic studies have been inconsistent. Theoretically, an association between NHL and smoking is possible as tobacco smoke is known to contain substances considered to be leukemogens and experimental studies have shown effects on the immune system by tobacco smoke.[28] Evidence of such an association was first published in 1989 from an Italian hospital-based case-control study in which a non-significant increased risk (OR 1.5, 95% CI: 1.0, 2.3) for ever versus never smokers was observed.[76] An American cohort study of white male insurance holders found an age-adjusted relative risk of mortality from NHL of 2.1 (95% CI: 0.9, 4.9) for smokers compared to nonsmokers, with a gradient between number of cigarettes ever smoked per day.[77] However, most other large cohort and case-control studies of cigarette smoking and cancer have demonstrated little association of smoking with NHL.[12] In a recent critical review of the literature, Peach and Barnett concluded that the weight of

evidence did not suggest an association but that the results of many of the studies may have been affected by biases, confounding, or lack of recognition of NHL as a heterogeneous disease.[78]

2.2.5.4 Diet

There is no established association between any dietary component and NHL risk,[28] although some analytical studies have suggested that milk, red meat, butter, liver, and ham may be associated with increased risk; and fruit, carrots, and whole grain dietary products with a decreased risk.[12] For example, in the Nurses' Health Study cohort, a lower risk of NHL was associated with higher intake of fruits and vegetables. The relative risk was 0.6 (95% CI: 0.4, 1.0) for women who consumed six or more servings per day as compared with those consuming less than three.[79]

2.2.5.5 Alcohol

As reported by Melbye and Trichopoulos, there is a limited literature and no support for alcohol intake as risk factor for NHL.[28]

2.2.5.6 Anthropometric Measures

The literature on the relationship of anthropometric measures with NHL risk is limited, although some studies have demonstrated a positive association of body mass index (BMI) with NHL. In a case-control study in the San Francisco Bay area that assessed a large number of lifestyle, demographic, and medical history factors, the risk of NHL increased with increasing level of BMI, with an odds ratio of 3.1 (95% CI: 1.4, 6.8) in females and of 2.6 (95% CI: 1.2, 5.7) in males for those with BMI 30 kg/m^2 or greater relative to those with BMI less than 20 kg/m^2.[80] In a prospectively studied cohort of 900,000 American adults, higher rates of death due to NHL were observed in those subjects with higher a BMI compared those with a BMI within the normal range

after adjustment for a number of potential risk factors (RR 1.6, 95% CI 1.3, 1.9 in males and RR 1.2, 95% CI 1.0, 1.5 in females for those with BMI 30-35 kg/m^2 relative to those with BMI 18-25 kg/m^2).[81]

2.2.6 Chemical and Physical Agents

2.2.6.1 Pesticides

Non-Hodgkin's lymphoma has been linked with exposure to pesticides, including phenoxy acid and chlorophenol herbicides (particularly 2,4-dichlorophenoxyacetic acid) and organophosphate pesticides.[28] In a population-based case-control study in Kansas, the use of phenoxyacetic acid herbicides was associated with a notable dose-response effect for NHL with an overall OR of 1.6 (95% CI: 0.9, 2.6) for farmers using herbicides relative to non-farmers, but an OR of 6.0 (95% CI: 1.9, 19.5) for those using herbicides for more than 20 days per year, and of 8.0 (95% CI: 2.3, 27.9) for those mixing and applying herbicides themselves.[82] In another case-control study in farmers, the use of 2,4-dichlorophenoxyacetic acid for more than 20 days per year was associated with an increased risk of NHL (OR 2.4). Independent of the effects of 2,4-dichlorophenoxyacetic acid, the use of organophosphate insecticides was also associated with an increased risk of NHL (OR 2.4).[83] In a study based upon the Canadian National Enhanced Cancer Surveillance System (the data source for our research), an increased risk of NHL among men was found with self-reported work with both pesticides (OR 1.3, 95% CI: 1.0, 1.6) and herbicides (OR 1.3, 95% CI: 1.0, 1.6); and among women with work with pesticides (OR 1.4, 95% CI: 1.0, 2.0).[84] A cohort study of male Saskatchewan farmers using record linkage found a significant dose-response relationship between NHL mortality and acres sprayed with herbicides, with a relative risk of 2.2 (95% CI: 1.0, 4.6) for the

highest level of herbicide use (≥250 acres sprayed).[85] In an update of this study, based on three Canadian prairie provinces and a longer duration of follow-up, a relative risk of 2.1 (95% CI: 1.1, 3.9) was observed for farmers spraying 380 acres or more with herbicides.[86] A possible mechanism is suggested by reports of chromosomal rearrangements associated with pesticide application.[28] In a case-control study of rural men in Iowa and Minnesota, an association of NHL with several agricultural pesticides (but not with the phenoxy acid herbicides) was found only for those lymphomas with a t(14;18) translocation.[87] However, Melbye and Tricholoupos have noted that, since agricultural occupations involve outdoor work, these associations may be confounded by exposure to ultraviolet light, which has also been considered a potential risk factor for NHL.[28]

2.2.6.2 Benzene

Benzene is a monocyclic aromatic hydrocarbon[88] used in industry as a volatile solvent in paint and rubber products and in the production of solvents, dyes, explosives, and resins used in the manufacture of plastics, elastomers, and textiles.[89] It is a natural component of petroleum and a constituent of gasoline. By the respiratory route, benzene has been shown to cause effects on both humeral and cellular components of the immune system.[89] In 1981, the International Agency for Research on Cancer (IARC) classified benzene as a human carcinogen in view of the epidemiologic evidence linking benzene exposure with acute myeloid leukemia.[90] However, its role in relation to other hematopoietic malignancies is less well established. Lymphomas were associated with benzene exposure as early as 1979. In a study based on job titles and diagnoses on death certificates in men from New York State, a relative risk of 2.0 (95% CI: 1.8, 2.1) for the association of lymphosarcoma with benzene exposure was observed.[91] In a

population-based case-control study from France, an association between self-reported exposure to benzene and NHL was observed (OR 2.0, 95% CI: 1.1, 3.9), with a consistent dose-response relationship.[92] In a large cohort study of Chinese factory workers with average benzene exposure of 23 ppm in those exposed, a non-significant increased risk of NHL with benzene exposure (RR 3.0, 95% CI: 0.9, 10.5), with a dose-response for duration of exposure, was found.[93] However, other studies, including some large, well designed studies have shown no increased risk. For instance, in a large population-based case-control study of cancer and occupational exposures from Montreal, odds ratios of 0.6 (95% CI: 0.4, 1.0) and 0.8 (95% CI: 0.4, 1.6) were reported for the association of NHL with low and medium/high benzene exposure relative to no exposure, respectively.[88] After a systematic review of the epidemiologic literature on benzene and lymphatic and hematopoietic cancers in 1997, Savitz and Andrews concluded that benzene exposure was generally not associated with an increased risk of NHL.[94]

2.2.6.3 Ionizing Radiation

Interestingly, the evidence that NHL is increased following exposure to ionizing radiation is weak and inconsistent, while that for leukemias, excluding chronic lymphocytic leukemia (CLL), is very strong. Boice[95] reviewed the epidemiologic literature of NHL and leukemia risk in populations exposed to ionizing radiation; a summary of his findings follows. NHL has rarely been found to be associated with radiation, and no study has demonstrated a dose-response relationship. Early studies of atomic bomb survivors suggested an association of radiation with NHL, but later studies with longer follow-up did not confirm this association. In one study, relative risks of 0.95 for NHL and of over 6 for leukemia at 1 gray (100 rads) whole body exposure were

reported. The occurrence of NHL is frequently found to be increased following treatment for Hodgkin's disease, but this increase appears to be independent of treatment with radiation. One of the few studies where radiation may have been related to NHL risk involved exposure to Thorotrast, a radiographic contrast media used in the 1930s and 1940s for angiography, where a nearly 3-fold nonsignificant risk for NHL was reported. Thorotrast emits alpha-particles and remains in the body for life and could potentially result in very high radiation doses to lymph nodes. Occupational studies have provided no evidence of an association. For example, in a study of over 27,000 radiologists in China, no excess of lymphoma was found, while a relative risk of 3 was observed for leukemia.

In addition, significantly increased risk of NHL has not been found in more recent occupational studies carried out in Canada. In a cohort study of occupational radiation exposure based on dose information from the National Dose Registry of Canada, in the analysis of cancer incidence, a nonsignificant excess relative risk of 6.6 per sievert (Sv) in males and females combined for NHL was reported.[96] In the analysis of mortality, excess relative risks of -0.9 per Sv in males and of -0.2 per Sv in females for NHL were reported.[97]

2.2.6.4 Power Frequency Magnetic Fields

Although widely debated, it is possible that exposure to power frequency magnetic fields (MF) increases the risk of NHL. The evidence regarding such an association is reviewed in Section 2.4 and is added to by the results of this research project.

2.2.7 Summary

In summary, the well established risk factors for NHL include: factors associated with immune dysfunction (immunodeficiency and autoimmunity); the infectious agents HIV, EBV, and HTLV-1; and gender and age. Although we do not have data for the risk factors associated with immune dysfunction and infectious agents in our case-control study of NHL, these factors are not prevalent in Canada. Therefore, while it is possible that these factors are associated with exposure, we consider it unlikely that they will result in important confounding in our assessment of NHL risk associated with occupational exposure to MF. Risk factors for which we have data in our study and for which there is evidence suggestive of an association with NHL include pesticides and benzene; and for which there is less evidence of an association with NHL include cigarette smoking, socioeconomic status, and ionizing radiation. These factors were considered for inclusion in our study analyses. Factors for which we have data available in our study but for which there is little or no evidence of an association with NHL include alcohol, anthropometric measures, and diet. These factors were not considered for inclusion in our study analyses.

2.3 Electromagnetic Fields and Cancer

Overview

Extremely low frequency (ELF) electromagnetic fields have been shown to have some biological effects and have been associated with certain malignancies in epidemiologic studies. The potential mechanisms and the evidence from toxicological, clinical, and epidemiologic studies pertaining to the potential carcinogenicity of magnetic fields (MF) are reviewed below.

2.3.1 Potential Mechanisms

Potential biological mechanisms through which ELF MF may cause cancer include the following: [2 41 98 99]

- direct or indirect damage to DNA;
- induction of mutations;
- effects on gene transcription or translation;
- alteration of signal transduction pathways which help regulate cellular processes such as gene expression, metabolic activity, differentiation, or proliferation;
- disruption of the normal circadian rhythm of melatonin, a hormone produced by the pineal gland which may have anti-tumor effects; and/or
- effects on the immune system.

The possibility that electric and/or magnetic fields may cause cancer through effects on the diurnal rhythm of circulating melatonin levels was raised by Stevens[100] in 1987. In mammals, melatonin levels rise at night and fall during the day in response to exposure to light. The most recognized function of melatonin is in the regulation of seasonal reproductive activities in certain species. It has been reported that: a) exposure to ELF MF suppresses the production and secretion of melatonin from the pineal gland in rodents;[41] and b) that melatonin is oncostatic in animal models of breast cancer.[101] In addition, melatonin has been shown to be a potent scavenger of free radicals, suggesting that melatonin suppression could increase the probability of genotoxicity and thus cancer risk.[101]

It is well known that ELF electromagnetic fields do not have sufficient energy to break chemical bonds or to cause tissue heating.[102] However, these fields may act as control signals to modify processes that depend on metabolically supplied energy.[1 (p. 29)]

Biophysical mechanisms that have been proposed to explain the interaction of MF with biological systems include: [2 39 41 98 99 103]

- magnetic induction of electric currents at cell membranes and in tissue fluids;
- direct magnetic force effects on either moving ions or on ferromagnetic particles in human cells;
- effects on the flow of ions across cell membranes or on chemical reactions due to resonances that depend on complex interactions between static and oscillating magnetic fields;
- MF effects on free radical pair formation; and
- induction of slight changes in the average frequency of events that trigger other processes (i.e., spatial or temporal signal averaging mechanisms).

From a biophysical standpoint, these theoretical mechanisms lead to the conclusion that biological effects below exposures of 100 μT are unlikely.[2] However, it should be noted that each of these potential mechanisms suffers from serious theoretical difficulties and/or lack of experimental support in living systems at relevant exposures.[99] In addition, it should be remembered it is well established that some animals, including eels, sharks, and pigeons, are able to detect extremely weak MF; thus at least some specialized cells must be sensitive to these fields.[102] Furthermore, there is strong evidence from randomized controlled trials that clinical exposures to pulsed electromagnetic fields have a significant effect on the primary bone healing process.[2 (p. 401)] As argued by Savitz *et al*, the biological mechanisms for several known environmental carcinogens (e.g., arsenic and benzene) were not established in the laboratory until several years after their firm establishment as carcinogens in epidemiologic studies.[104] Thus, lack of knowledge regarding the mechanism of action

does not preclude the possibility that low levels of electromagnetic fields have biological and possibly carcinogenic effects.

2.3.2 Toxicologic Studies

2.3.2.1 In vitro Studies

In vitro studies of ELF MF exposure have shown these fields to have some biological effects, but only at intensities much higher than those generally encountered in the environment.

A Working Group for the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health reviewed data pertaining to potential health effects of exposure to power-line frequency electric and magnetic fields in 1998. This group reported that "numerous well-performed in vitro studies have shown strong effects on end-points commonly associated with carcinogenic agents", including significantly increased cell proliferation, disruption of signal transduction pathways, and inhibition of differentiation. However, all of these effects were demonstrated at field intensities greater than 100 μT.[2] (pp. 354-5)

In addition, this Working Group reported that a series of studies has shown that intense MF exposure induced gene mutations. Although ELF fields at flux densities below 100 μT have consistently shown no effect on mutation rates, fields of 200-400,000 μT have reproducibly and significantly enhanced mutation rates after initiation with ionizing radiation. In addition, exposure to 400,000 μT with no initiating exposures has resulted in an increase in the number of mutations in two human cell lines. However, in a review of the literature by McCann *et al*[105], it was concluded "the preponderance of evidence suggests that electric or magnetic fields do not have

genotoxic potential". This appears to be the general consensus of the scientific community.

2.3.2.2 Animal Studies

Animal studies generally suggest a lack of carcinogenicity.[2 (pp. 85-106)] As reported by the NIEHS Working Group, at least three experimental studies of life long exposure to power frequency MF have been conducted in rodents. These studies involved either rats or mice exposed to 50 or 60 Hz MF ranging from 2 to 5,000 μT. With the exception of isolated thyroid C-cell adenomas and carcinomas in male rats in one study, no significant effects of exposure on cancer development were seen.[2 (p. 89)]

The NIEHS Working Group also reported that studies of leukemia/lymphoma models in rats or mice have been conducted with: exposure to MF after induction of leukemia/lymphoma by initiation with X-rays or a chemical carcinogen; or progression of the disease under the influence of power frequency MF after introduction of leukemia cells into the animal. Fifty or 60 Hz MF of 1,000 to 1,400 μT were applied for 18 weeks to two years. These fields did not promote leukemia or lymphoma.[2 (pp. 98-102)]

Although these studies suggest a lack of carcinogenicity in animals, it should be noted that they have been conducted at MF exposure levels well below those that would correspond to a maximum tolerated dose (MTD) (which is the usual dose used in toxicity studies for risk assessment) yet at levels much above those encountered by the human population.[99] Further, most of the investigations carried out have followed the pattern of the traditional testing of chemical agents suspected to be carcinogenic. It is possible that investigations of the role of MF in carcinogenesis may require different approaches, such as the use of models that combine chronic exposure to both MF and known carcinogens.[2 98]

2.3.3 Controlled Studies in Humans

There have been few controlled studies in humans of exposure to power frequency MF and these have had mainly negative results. However, it should be noted that these results have been based upon short-term exposures in mainly healthy young men.[2] (pp. 312-4)

As described in section 2.3.1, one potential mechanism of carcinogenicity of MF is through an effect on melatonin, a hormone produced by the pineal gland and which is thought to have anti-tumor effects. The NIEHS Working Group reported that six controlled laboratory studies of the effects of night time exposure to 50 or 60 Hz MF of 1 to 20 μT on blood concentrations of melatonin and its urinary metabolite have been carried out on human volunteers.[2] (pp. 311-3) In five of these studies, no nocturnal suppression of melatonin with MF exposure was observed, while in one a possible delay in peak onset of melatonin blood levels with exposure was observed.[2]

Another potential mechanism of carcinogenicity of MF is through effects on the immune system. Three controlled studies are reported by the NIEHS Working Group to have examined the effects of power frequency MF exposure on immune function in human volunteers, with none showing any changes in blood counts, lymphocyte subtypes counts, and/or circulating stress hormones.[2]

2.3.4 Epidemiologic Studies

The first evidence that electromagnetic fields may be related to cancer mortality was obtained in 1979, when a study published by Wertheimer and Leeper[106] suggested an association between residential exposure to power frequency MF and increased cancer risk in children. The first suggestion that occupational exposure to

electromagnetic fields increases cancer risk was from a proportional mortality analysis published by Millham[107] in 1982 in which an excess number of leukemia deaths were reported in electrical workers. Since that time, numerous other epidemiologic studies have been carried out with a fairly consistent demonstration of a small but significant increased risk of childhood leukemia associated with residential MF exposures and of a small but inconsistent risk of adult chronic lymphocytic leukemia (CLL) with occupational MF exposures. A brief summary of these results follows.

2.3.4.1 Residential Exposure and Leukemia in Children

In the case-control study of childhood cancer published by Wertheimer and Leeper[106] in 1979, residential MF exposure was categorized based upon the wiring configurations of the power lines outside the residence. The categorizations were referred to as wire codes. The risk of leukemia for children living in homes with high wire codes was 3.0 times (95% CI: 1.8, 5.0) that for children living in homes with low wire codes. Elevated risks were also observed for lymphomas (OR 2.1, 95% CI: 0.8, 5.2) and nervous system tumors (OR 2.4, 95% CI: 1.2, 5.0). The results of this study led to much subsequent research on the issue, with improvements in the methodology, including improved exposure and confounder assessment, and improved control selection. Presumed improved exposure assessments included spot measurements and 24-hour measurements of MF within the home, although paradoxically many studies using exposure assessments based on these field measurements did not find an association. This came to be known as the wire code paradox. Improved control selection was realized through use of population registries and complete population data available in certain Scandinavian countries.

Recently two pooled analyses[108] [109] of this research have been published; in both an increased risk for the highest level of exposure relative to the lowest level, but not for the mid levels, was found. The results were consistent across studies, with the use of different exposure metrics or different cutpoints, and with adjustment for socioeconomic factors. In both analyses, the conclusion was made that the observed effect was unlikely to be due to chance. However, the possibility that these observed effects were due to confounding and/or especially selection bias was considered difficult to rule out. Although adjustment for socioeconomic variables did not materially affect the results, it has been suggested that traffic density effects and ambient pollution levels may partly explain the observed associations.[109] More importantly, given the low response rates in many of the studies and difficulties with control selection methods in some, it is impossible to rule out the possibility that the observed associations are due to selection biases.

The pooled analysis of Alhom *et al*[108] was based on nine well conducted studies completed before 2000 and used individual records for the 3,247 cases of leukemia and 10,400 controls included in these studies. Exposure was assessed by either 24- to 48-hour indoor MF measurements or calculations of historical exposures of MF. The primary exposure metric was the geometric mean MF exposure and the highest cutpoint in the exposure categories was 0.4 μT. No increased risk was found for children in the intermediate categories of exposure, but a 2-fold increased risk was observed for the 44 children with leukemia and 62 control children with estimated residential exposures of 0.4 μT or greater relative to those with estimated exposures of less than 0.1 μT (OR 2.0, 95% CI: 1.3, 3.1). They also analyzed the association of wire codes with leukemia in the two North American studies. The risk associated with the highest relative to the

lowest wire code in the combined North American data was 1.2 (95% CI: 0.8-1.9). Therefore, as this risk based on the surrogate measure was lower than the risk based on the direct estimates of the MF, this pooled analysis provided no evidence to support the existence of the wire code paradox.[108]

The pooled analysis of Greenland *et al*[109] used less restrictive inclusion criteria. It was based on individual data from 15 studies, 12 of which included MF exposure estimates based on calculated fields or on direct measurements, either spot measurements or 12- to 48-hour indoor measurements. The primary exposure metric was the time-weighted average MF and 0.3 μT was the highest cutpoint in exposure categories. In the twelve studies with measurement data for a total of 2,656 cases and 7,084 controls, an increased risk was observed for those with exposure greater than 0.3 μT compared to those with exposure of 0.1 μT or lower (OR 1.7, 95% CI: 1.2, 2.3). The risk for those in the intermediate exposure categories was not observed to be elevated. They too also analyzed the association of leukemia with wire codes and found no evidence to support the wire code paradox. Wire codes showed a less consistent association with childhood leukemia than did measured MF. The results were heterogeneous across studies (homogeneity p=0.005), with odds ratios for very high current configurations versus low current configurations ranging from 0.7 to 3.0. In addition, adjustment for measured fields in the analysis of the four studies with both wire code and measurement data did not reduce the association of wire codes with childhood leukemia.[109]

2.3.4.2 Occupational Exposure and Chronic Lymphocytic Leukemia

In the proportional mortality study published by Millham[107] in 1982, which was the first study to suggest a possible association between cancer and occupational

electromagnetic field exposure, an excess of leukemia deaths in 'electrical workers' was found among men in Washington State from 1950 through 1979. The proportional mortality ratio was 1.4 for all leukemia and 1.6 for acute leukemia, both with reported p-values of <0.01. Electrical workers included electronic technicians, radio and telegraph operators, electricians, telephone and electric utility linemen, television and radio repairmen, power station operators, aluminum workers, welders and flame cutters, motion picture projectionists, electrical engineers, and streetcar and subway motormen. It was inferred that these electrical jobs were associated with exposure to elevated levels of electromagnetic fields. Since then, over a hundred epidemiologic studies of occupational exposure to electromagnetic fields and various diseases have been carried out,[2 (p. 108)] with improvements made in exposure and potential confounder assessments and the use of more reliable epidemiologic study designs.

Various groups have attempted to summarize the results of these studies. In 1998, the NIEHS reviewed the epidemiologic literature of electromagnetic fields and cancer and concluded "there is limited evidence that occupational exposure to ELF magnetic fields is carcinogenic to humans on the basis of results of studies of chronic lymphocytic leukemia." [2 (p. 396)] However, in the more recent review by the International Agency for Research on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans in 2002, it was concluded that there is inadequate evidence for the carcinogenicity of ELF MF in relation to all cancers except childhood leukemia.[3 (p. 338)] In 1997, a meta-analysis[110] was carried out based on 38 studies reporting results for leukemia and occupational exposure to MF. The overall odds ratio for leukemia was 1.2 (95% CI: 1.1, 1.2); and for the 12 studies reporting results for CLL, the overall odds ratio for CLL was 1.6 (95% CI: 1.1, 2.2). There was evidence of significant

heterogeneity in the results for CLL in the different studies that assessed this subtype, but less so in the results for all leukemias in all studies included in the meta-analysis. Sources of heterogeneity in the results for all leukemia subtypes among studies identified included: exposure assessment based upon complete work histories and/or measurements with these studies tending to show a lower risk; and better assessment and adjustment for confounders, with these studies tending to show an increased risk.

While the IARC conclusion regarding leukemia and occupational exposure was based on their observation that "there was no consistent finding across studies of an exposure-response relationship and no consistency in the association with specific sub-types of leukemia",[3 (p. 334)] the conclusion of the NIEHS was based on the results of the four studies of CLL they considered to be the best. (These studies were considered to be better than others in part because exposure assessments were based on full shift measurements of MF.) The four studies considered by the NIEHS in making their evaluation in regard to CLL included three studies of incidence (two in Sweden and one from Canada and France and one of mortality in the United States) and are described briefly below.

The first study considered was a population-based case-control study from Sweden carried out by Floderus *et al.*[111] In this study, an association between CLL risk with occupational MF exposure with an exposure-response was observed. Exposure was based on the mean MF level in the job held the longest in the ten-year period before diagnosis. The odds ratios were 1.1 (95% CI: 0.5, 2.3), 2.2 (95% CI: 1.1, 4.3), and 3.0 (95% CI: 1.6, 5.8) for mean exposures of 0.16-0.19 μT, 0.20-0.28 μT, and >0.28 μT compared to mean exposures of <0.16 μT. These results were not changed significantly by controlling for confounding by urban/rural place of residence, smoking, benzene,

ionizing radiation, pesticides, or solvents. The MF exposure assessments were based on reported occupation in questionnaires sent to subjects, 1,015 full shift measurements for 169 job categories, and use of a job exposure matrix. Of interest, in order to assess the effects of non-response, the analysis was repeated for all subjects, including those who did not respond to the questionnaire, based upon the subject's job indicated in the census. The odds ratios, although still increased, were reduced and no longer significant. These results were due in part to the larger proportion of unexposed subjects among non-respondents. These results suggest the possibility of a differential bias due to unexposed cases being less likely to respond than unexposed controls. This would have led to an overestimate of the risk in the respondents.[2]

The second study from Sweden was a population-based case-control study by Feychting *et al*[112] of leukemia and central nervous system tumors in which both occupational and residential exposures to MF were taken into account. An increased risk of CLL associated with MF exposure of ≥0.2 μT relative to exposures <0.13 μT was reported (OR 1.9, 95% CI: 1.0, 3.8). When the analysis was limited to those subjects with residential exposures of <0.2 μT, the risk of CLL in subjects with occupational exposures ≥0.2 μT was smaller (OR 1.5, 95% CI: 0.8, 2.7). Occupational MF exposure was based upon the subject's occupation listed in the census in combination with a job exposure matrix based on measurements carried out in the study of Floderus *et al.*[111] Residential exposure was based upon calculations of MF produced by power lines. Adjustment for potential confounding by exposure to motor fuel or exhaust, benzene, oil products, and welding fumes did not affect the results. Although these results were suggestive, interpretation is limited due to the small numbers of exposed in the study and lack of validation of the job exposure matrix in females.

The third study[113] considered was a case-control study nested within three large cohorts of male workers at electrical utilities (one each from France, Ontario, and Quebec). A non-significant increased risk of CLL was observed for workers with cumulative time-weighted average exposure to MF at or above the median (3.1 μT-years) compared to those with exposures below the median (OR 1.5, 95% CI: 0.5, 4.4, results adjusted for socioeconomic status). Cumulative exposure was estimated for each subject using a job exposure matrix based on measurements of current exposure in 2,066 workers using personal dosimetry for a five-day work week. Confounding was assessed for physical and chemical agents listed as carcinogenic or possibly carcinogenic by IARC, namely benzene, gasoline, paint, solvents, and ionizing radiation, without much effect on the results.

In the fourth study considered, Savitz and Loomis[114] found no association between leukemia mortality with cumulative time-weighted average MF exposure. This study was based on a historical cohort of 138,905 men employed at five large electric power companies in the United States between 1950 and 1986. Exposure was assessed by linking individual complete work histories from company records to data from 2,842 full shift MF measurements in 28 occupational categories. Exposure to potential occupational confounding factors including solvents, polychlorinated biphenyls, sunlight, and wood preservatives was evaluated. Vital status was determined through to 1988 for more than 99% of the cohort with diagnosis taken from death certificates. The odds ratios for CLL for exposures of 0.6 to <1.2 μT-years, 1.2 to <2.0 μT-years and >2.0 μT-years relative to exposures of <0.6 μT-years were 1.3 (95% CI: 0.5, 3.6), 2.0 (95% CI: 0.8, 5.1), and 0.6 (95% CI: 0.2, 1.1). Although this study was negative, it should be noted that the reliance on death certificates for diagnosis and the study of mortality

rather than incidence is particularly problematic in CLL given that it has a long survival time.

In summary, the epidemiologic evidence regarding leukemia and exposure to residential MF in children suggests a small increased risk that is consistent among studies but may be due bias; and the evidence regarding CLL and occupational exposure to MF suggests a possible small increased risk that is not entirely consistent among studies. While this evidence is not strong, it is difficult to discount the possibility that MF exposure may be related to the development of cancers of the lymphohematopoietic system.

2.4 Occupational Electromagnetic Field Exposure and Non-Hodgkin's Lymphoma

Although controversial, it is possible that exposure to power frequency MF increases the risk of non-Hodgkin's lymphoma (NHL). Given the recent increasing incidence in NHL, it is reasonable to hypothesize that unknown factors are associated with this cancer, some of which may be environmental.

It is generally assumed that individual exposure to MF in the general population has increased over the past 30 to 50 years due to changes in the generation and use of electricity.[115] The average exposure of the general population of England and Wales to MF as a result of residential background fields, domestic appliance use, and the transmission system has been estimated to have increased by a factor of 4.5 from 1949 to 1989.[116] However, others have suggested that it is unlikely the average MF exposure to individuals has risen substantially over the past 50 years despite the increased consumption of electricity, due to concomitant changes in wiring practices, voltages in transmission lines, and other factors.[104]

In addition to the possibility of increased exposure, there is evidence, as outlined in section 2.3, to suggest that ELF MF in residential environments are associated with leukemia in children and, in occupational settings, with chronic lymphocytic leukemia (CLL) in adults. Despite the fact that childhood leukemia, CLL, and NHL are each different diseases with differing etiologies, they have in common the feature that they are each malignancies of the lymphohematopoietic system and may therefore share some common etiological factors.

However, epidemiologic studies of NHL risk and occupational exposure to MF have produced inconsistent results.

2.4.1 Epidemiologic Studies Based on Job Titles

Some studies based on job titles have shown an increase risk of NHL for workers with job titles presumed to be indicative of elevated MF exposures, while others have not. For instance, Millham[117] reported, in an update of his original work on adult male death records in Washington State, a statistically significant proportional mortality ratio of 1.2 for all lymphatic and hematopoietic cancers grouped together in workers with presumed exposure to electromagnetic fields. In a study[118] based on death certificates for white males from Massachusetts, significantly elevated standardized mortality odds ratios were reported. Relative to other non-cancer deaths, the odds ratio was 3.3 for lymphosarcomas in electricians and 3.0 for all lymphomas in electrical engineers. In a Swedish study[119] in which data from the national Cancer-Environment Registry from 1961 to 1979 were linked with occupational information from the 1960 census, a significantly elevated standardized incidence ratio of 4.7 for NHL in men employed as engineers or technicians working in electric power plants relative to the

general population was found. In a case-control study[120] of NHL based on death certificates from 24 states in the United States with controls selected from deaths other than cancer, mortality odds ratios of 2.1 (95% CI: 1.1, 4.1) were reported for electronic repairers among white males and 2.1 (95% CI: 0.8, 5.8) for welders among black males. In contrast, in a case-control study[121] from New Zealand based on cancer registry data which included information on the registrant's current or most recent occupation, no increased risk of NHL relative to other cancer sites was found for male electrical workers (OR 0.8, 95% CI: 0.4, 1.4). In a cohort of male workers in Norwegian hydroelectric power companies with job titles indicating exposure to electromagnetic fields, the standardized incidence ratio for lymphomas with the Norwegian male population as the reference was 0.7 (95% CI: 0.4, 1.2).[122]

2.4.2 Epidemiologic Studies Based on Measurements

Studies in which exposure assessments have been based upon complete job histories within electrical utilities and full shift personal dosimetry measurements, and thus considered more reliable, have also produced inconsistent results.

Schroeder and Savitz[123] assessed the association between NHL, Hodgkin's disease, and multiple myeloma mortality and occupational exposure to MF in a retrospective cohort study of 138,905 electrical utility workers from five companies in the United States. This study was based on the same cohort of workers as the study of Savitz and Loomis[114] of leukemia and brain cancer described in Section 2.3. Individual estimates of cumulative exposure to MF, based upon the time-weighted average arithmetic mean, were derived from the individual's complete job history from company records using a job exposure matrix. This matrix was based upon full shift personal

monitoring device measurements made on a random sample of 2,842 current workers from 28 different occupational categories. Outcome was obtained from death certificates. A total of 154 cases of NHL were observed. Potential confounding factors included social class, race, age, and solvent exposure. In the analysis based upon job title and duration, small positive associations of both NHL mortality and the subtype low-grade NHL with employment in any MF-exposed job were observed. The relative risks for NHL varied between 1.2 (95% CI: 0.7, 2.0) and 1.4 (95% CI: 0.8, 2.4) for differing job durations. For the subgroup of low-grade NHL, the risk, relative to those subjects who had never held an exposed job, for subjects who had held any exposed job for less than 10 years was 2.6 (95% CI: 1.1, 6.3) and for subjects who had held any exposed job for 10 to 20 years was 2.7 (95% CI: 1.0, 7.1). However, for subjects who had held an exposed job for more than 20 years, the risk was 0.9 (95% CI: 0.3, 3.10). In the analysis based upon cumulative MF exposure, a small increase in NHL mortality was observed for workers with cumulative exposures above the referent category, but there was no dose-response seen over the five increasing categories of exposure. The relative risks of dying from NHL for workers with cumulative exposures of 0.6-1.2 μT, 1.2-2.0 μT-yrs, 2.0-4.3 μT-yrs, and >4.3 μT-yrs, relative to those with exposure <0.6 μT-yrs, were 1.5 (95% CI: 0.9, 2.4), 1.8 (95% CI: 1.1, 2.9), 1.8 (95% CI: 1.1, 3.1), and 1.3 (95% CI: 0.7, 2.8), respectively. The rate ratios for the subgroup of intermediate/high-grade lymphomas were 1.3 (95% CI: 0.4, 4.3), 3.7 (95% CI: 1.3, 10.4), and 2.3 (95% CI: 0.8, 6.9) for subjects with cumulative MF exposures of 0.6-1.2 μT-yrs, 1.2-2.0 μT-yrs, and >2.0 μT-yrs relative to those having exposure <0.6 μT-yrs, respectively. Risk was also assessed within different exposure time windows; risks were most pronounced for exposures occurring within the past 10- to 20-year time window. There were no

associations found between either Hodgkin's disease or multiple myeloma and MF exposure. The authors concluded that the results provide "some support for a weak association between occupational magnetic field exposure and NHL, particularly within intermediate- and/or high-grade subtypes". Limitations of this study include its reliance on death certificates for diagnosis, outcome based upon mortality cases rather than incident cases, and the relatively small numbers of cases.

Sahl *et al*[124] evaluated cancer mortality for lymphoma, leukemia, and brain cancer in a cohort of 36,221 workers from an electric utility in California using both cohort and nested case-control analyses. Magnetic field exposure was measured for a total of 776 person-days in 35 occupational categories in a sample of the current workforce using personal monitoring devices. Cumulative exposure was assessed by linking job history data with these measurements for the case-control analysis. Various exposure metrics were modeled including the arithmetic mean, the geometric mean, the 95th and 99th percentiles, and the fraction of time spent above 1.0 and 5.0 μT. Cumulative index scores and a variety of latency windows were analyzed. Outcome was determined from death certificates obtained through data linkages with vital status and cause of death information. Controls were matched on age, gender, and race. No other information was available for adjustment of potential confounding. A total of 67 cases of lymphoma were observed. In the cohort analysis, electrical workers were compared to all other workers, with an observed age-adjusted rate ratio for lymphomas of 1.3 (95% CI: 0.7, 2.3). In the case-control analysis, odds ratios were all close to 1 for lymphomas for exposure as an electrical worker and for various exposure scores. For example, the odds ratio for lymphomas for ten years exposure as an electrical worker was 1.0 (95% CI: 0.8, 1.2) and for 250 mG-yrs (25 μT-yrs) of cumulative mean MF

exposure was 1.0 (95% CI: 0.8, 1.4). The authors reported that they found no consistent association of death from lymphomas with either a history of working in electrical occupations or with measured MF. They concluded that while their results provide little information on the question of small effects, they do seem to exclude very large effects and are consistent with no effect from electric or magnetic field exposure on lymphoma occurrence. Limitations of this study include its reliance on death certificates for diagnosis, outcome based upon mortality cases rather than incident cases, the broad grouping of all lymphomas together (NHL, Hodgkin's disease, and multiple myeloma), lack of adjustment for potential occupational confounding factors, a relatively small number of cases, and the inability to identify some cases occurring outside of California.

Theriault's *et al*[113] study of cancer risks associated with occupational exposure to MF, also described in Section 2.3 in regard to the results for CLL, included an evaluation of the risk of NHL. This study used a case-control design nested within a cohort of a total of 223,000 workers at three electric utilities (Electricite de France-Gaz de France, Ontario Hydro, and Hydro-Quebec). Cumulative exposure to MF was based on measurements made by personal dosimetry for a five-day work week in a sample of 2,066 current workers. Incident cases of cancer were identified through company medical files, the Quebec Tumor Registry, and death certificates for the Quebec utility; through the Ontario Cancer registry for Ontario Hydro; and through a company file of employee absences of active employees for the French utility. Adjustment was made for socioeconomic status. Occupational exposure to chemicals did not result in any apparent confounding of the results, although those assessed in the analysis of NHL risk were not actually specified. A total of 160 cases of NHL were observed. The odds ratio

for those with cumulative MF exposure at or above the median value of 3.1 μT-yrs compared to those with exposure below the median value was 1.2 (95% CI: 0.8, 1.9); and for those with cumulative exposure at or above the 90th percentile (15.7 μT-yrs) compared to those with exposure below the median value was 1.1 (95% CI: 0.5, 2.3). As NHL was not a major endpoint of interest in this study, the authors did not make any conclusions with regard to NHL risk. Limitations of this study include differences in study protocols between the three utilities (particularly the limited follow-up of subjects from the French utility, i.e., no follow-up of subjects after retirement) with differing results between the three utilities, and the relatively small number of cases.

Miller *et al*[125] further analyzed the data from the Ontario Hydro component of the tri-utility study described above. Evaluations of associations of NHL risk and both cumulative electric field exposure and cumulative MF exposure were made based upon 51 cases of NHL that occurred within the cohort of 31,543 male workers. Cases were ascertained by linkage with the Ontario Cancer Registry. Exposure was determined by use of a job exposure matrix that took into account job title, work location, and calendar time. The matrix was created for 17 job categories, 11 of which were stratified by 15 work site locations, and was based on the arithmetic mean of personal measurements from 895 current workers for five working days. Controls were matched for age and adjustments were made for socioeconomic status, year of first hire, and occupational exposure to chlorophenoxyacetic acids. The odds ratio for NHL and cumulative MF exposure for the middle tertile (3.2-7 μT-yrs) compared to the lowest tertile (≤ 3.1 μT-yrs) was 1.4 before adjustment and 1.3 (95% CI: 0.54, 3.0) after adjustment; and for the upper tertile (≥7.1 μT-yrs) was 1.8 before adjustment and 1.3 (95% CI: 0.46, 3.6) after adjustment. Higher but again not statistically significant odds ratios were seen in

the evaluation of the association of NHL with cumulative electric field exposure. The odds ratio for NHL for the middle tertile of cumulative exposure (172-344 V/m-yrs) compared to the lower tertile (0-171 V/m-yrs) was 1.7 before adjustment and 2.1 (95% CI: 0.69, 6.6) after adjustment; and for the upper tertile (≥345 V/m-yrs) was 2.1 before adjustment and 2.4 (95% CI: 0.72- 8.3) after adjustment. Of interest, in the evaluation of leukemia, a dominant effect of electrical field exposure was observed when both electric and magnetic field exposures were considered together. There was an increased risk of leukemia for increasing exposure to electric fields at each level of exposure to MF, while there was no consistent change in the risk of leukemia with increasing exposure to MF within levels of electric field exposure. A similar analysis was not presented for NHL. The authors concluded that their study supported an association between estimated exposure to MF and certain types of leukemia (specifically acute myeloid leukemia) and that the association may be driven by concomitant exposures to electric fields rather than MF. They did not comment on their results for NHL as this was not a major outcome of interest in their analysis.

Villeneuve *et al*[115] also further analyzed the data from the Ontario Hydro component of the tri-utility study. Their primary objective was to examine the association between the incidence of NHL and exposure to 60 Hz electromagnetic fields using a series of indices measuring different aspects of field strength. Risks were adjusted for total duration of employment, socioeconomic status, and occupational exposure to benzene and to chlorophenoxy acetic acids. For the most part, there was a lack of association between exposure indices of MF and NHL, while there was an association between NHL risk and the percentage of time spent working in areas with electric field intensities above 10 and 40 V/m. The risk of NHL was greater for subjects

who spent more than 15% of their working time exposed to electric fields above 10 V/m relative to those who spent less than 11% of their working time exposed to these fields (OR 3.1, 95% CI: 1.1, 8.8); the risk for those who spent more than 4.8% of their working time exposed to electric fields above 40 V/m was 3.6 times that of subjects who spent less than 2.8% of their occupational time exposed at this level (95% CI: 1.3, 9.8). The authors concluded that "this study suggests that electric fields, particularly exposures received above a threshold are associated with an increased risk of NHL" and supports the hypothesis that electric fields play a promoting part in the etiology of NHL.

The studies of Villeneuve *et al* and of Miller *et al* described above suggest that electric field exposure may be more important predictors of NHL than MF exposure. In addition, the study of Villeneuve *et al* suggests that other exposure metrics (such as exposure above a threshold intensity) may be more important predictors of NHL than duration of exposure and mean exposure.

Johansen and Olsen[126] reported the incidence of cancer in a cohort of 32,006 (26,135 men and 5,871 women) employees from all 99 electric utility companies in Denmark and compared them with the national incidence rates of cancer by sex, five-year age group, and calendar year period. Employment history was obtained from work records of the electric utility companies and exposure was assigned using a job exposure matrix. This matrix included the average level work day exposure to 50 Hz MF for 475 unique combinations of 25 different job titles in 19 different work areas. Exposure levels were based partly on a series of 196 24-hour personal dosimetry MF measurements from 129 employees in six of the utilities and partly on the expert judgement of four company engineers. The personal dosimetry measurements had been carried out as part of an earlier study.[127] Exposures were categorized as background (<0.09 μT), low

(0.1-0.29 μT), medium (0.3-0.99 μT), high (>1.0 μT), and unknown. Cancer incidence was ascertained through record linkage to the Danish Cancer Registry for the years 1968 through 1993. A total of 52 cases of NHL were observed: 48 in the men and 4 in the women. The standardized incidence ratio for men was 0.9 (95% CI: 0.6, 1.1) and for women was 0.7 (95% CI: 0.2, 1.7). Results of analysis by level and duration of exposure were not presented for NHL. The authors concluded that their study "does not support the hypothesis of an association between occupational exposure to EMFs and the risk for cancer". Limitations included lack of data to allow adjustment for possible confounding variables, a less comprehensive exposure assessment, and comparisons with the general population rather than within the cohort. In addition, in the analysis for NHL, exposure level was not taken into account.

2.4.3 Summary of Epidemiologic the Evidence

In summary, the epidemiologic evidence supporting an association between the risk of NHL and exposure to MF is weak. However, the published epidemiologic studies suffer from one or more limitations. These limitations include: small numbers of cases; mortality cases rather than incident cases; diagnosis based upon death certificate information; broad groupings of heterogeneous diseases; exposure assessments based on job title rather than on measurements; exposure assessments based upon most recent job or occupation listed on death certificate rather than a complete occupational history; and/or limited data to control for potential confounding factors and assess potential effect modifiers. In addition, it is difficult to study the risk of NHL associated with MF in epidemiologic studies because it is unclear which exposure metric or time

window of exposure is relevant to risk. Furthermore, as NHL is a heterogeneous group of diseases, it is possible that risk is limited to certain subtypes.

2.5 Rationale for the Study

In our study of NHL and occupational exposure to power frequency MF, which is described in the following three chapters, we hoped to overcome some of the limitations of studies conducted to date in this area. Specifically, we had the advantages of a large number of incident cases of NHL, of information on subjects' complete occupational histories, and of information for many potentially confounding or effect modifying factors, including for example work with benzene or pesticides; smoking history; income status; and education level. We were able to carry out analyses for different subtypes of NHL because of both the large number of cases and the information available on histology within the NECSS for our study. Because our study sample was population-based, there was likely to be less selection bias in choosing controls than there would be in non-population-based case-control studies. In addition, as we had a complete occupational history for each subject, we were able to carry out analyses based upon cumulative measures of exposure and to explore the effects of different latency and exposure time window effects. Although our exposure assessments were not based upon direct measurements, they were made by an expert-assessment of occupational exposure in all jobs based on job information in addition to the simple job title. It should be noted that "even when measured magnetic field data are used to calculate exposure scores, job titles and the grouping of job titles into an occupational classification system are necessary to link measured field data to the occupational history information to estimate historical exposures"[124] and are thus still a surrogate for

the historical exposure of interest. Further, "day-to-day variation in work activities and exposure further attenuates the accuracy of a few days (or even a few weeks) of measurement data as a reflection of the long-term exposures of interest."[128]

CHAPTER 3
METHODS I: National Enhanced Cancer Surveillance System Case-Control Component

Overview

The Canadian National Enhanced Cancer Surveillance System (NECSS) was a collaborative project between Health Canada and the Provincial Cancer Registries.[129] The purpose of this project was to provide data for the evaluation of potential environment-cancer associations and to strengthen cancer surveillance in Canada. The three components of this system included a national community level environmental data base with information on air and water quality, a population-based cancer case-control study, and a geographic surveillance network examining areas of high and/or unusual patterns of cancer incidence. The case-control component was based on a national population-based sample of newly diagnosed cancer cases and population controls.

3.1 Selection of Cases and Controls

The cases were identified from provincial cancer registries in eight of the ten provinces in Canada over the time period 1994 to 1997. All cases were to have histological confirmation except for cases of pancreatic and brain cancer. Cases were sampled such that number of male and females cases was roughly equal for each cancer site (except for prostate and breast). The provincial registries identified NHL cases using pathology reports. Non-Hodgkin's lymphoma (NHL) was defined as International Classification of Diseases for Oncology Version 2 (ICD-O/2) morphology codes 9590 to 9595 and 9670 to 9723 with any topography code. Physician consent was obtained prior to approaching cases. After obtaining physician consent, registries sent a letter

and questionnaire to each subject. If the questionnaire was not completed and returned a reminder postcard was sent after two weeks, a second questionnaire was sent after four weeks, and telephone contact was attempted after six weeks at which time the subject was offered a telephone interview if desired. To address poorly completed questionnaires, the registry attempted to contact subjects by telephone using a structured calling protocol. Questionnaires were sent to cancer patients within one to four months of diagnosis. For certain cancers with short average survivals, proxy questionnaires were sent to next of kin for completion if the cancer patient was too ill or had died before a questionnaire could be completed. Proxy questionnaires were not sent for cases diagnosed with NHL. A total of approximately 26,000 cases with one of 19 types of cancer were included in the NECSS, including 1,666 cases of NHL.

The control group was a random sample of 5,039 individuals from the participating provinces. Controls were frequency matched to the overall case group of all cancers by sex and five-year age group category. Provinces were given a quota for the number of controls to be recruited in each sex-age group strata based upon their population size. Controls were collected over the calendar year 1996, with collection spread over the year to allow for an even distribution of exposures that may be affected by season. Provincial Cancer Registries collected the information from controls using the same protocol as for cases.

The sampling strategies used to identify controls varied by province. Provincial health insurance registration databases were used in British Columbia, Saskatchewan, Manitoba, Prince Edward Island, and Nova Scotia; the Ontario Ministry of Finance Property Assessment Database was used in Ontario; and random digit dialing was used in Alberta and Newfoundland. Provincial health insurance registration databases cover

more than 95% of residents. The random digit dialing protocols used by Alberta and Newfoundland were slightly different. In Alberta, the University of Alberta's Population Research Laboratory generated a random sample of provincial telephone numbers including unlisted numbers. In Newfoundland, Newfoundland Telephone provided the local cancer registry with a random sample of Newfoundland phone numbers, including unlisted numbers. In both provinces, each randomly selected phone number was called up to eight times on a pattern structured around call attempts during the day, evenings and on Saturday.

3.2 Response Rates

A total of 2,563 NHL cases were ascertained. Physicians refused consent to contact 6.9% of cases and 10.8% of cases were deceased before they could be contacted. Completed questionnaires were received from 1,666 NHL patients (76.3% of women and 75.1% of men who were sent questionnaires, and 65.0% of total cases ascertained).

Questionnaires were mailed to 8,060 individuals selected as potential controls. For 573 potential controls (7.1%), the mailed questionnaire was returned to the registry indicating a wrong address and no updated address could be found through publicly available sources. In total, 5,039 selected controls completed and returned the questionnaire (70.2% of women contacted, and 64.6% of men contacted, overall, 62.5% of controls ascertained).

In the two provinces (Alberta and Newfoundland) in which random digit dialing protocols were used to obtain population samples, individuals were selected as potential controls after their identification through telephone census; thus response rates from

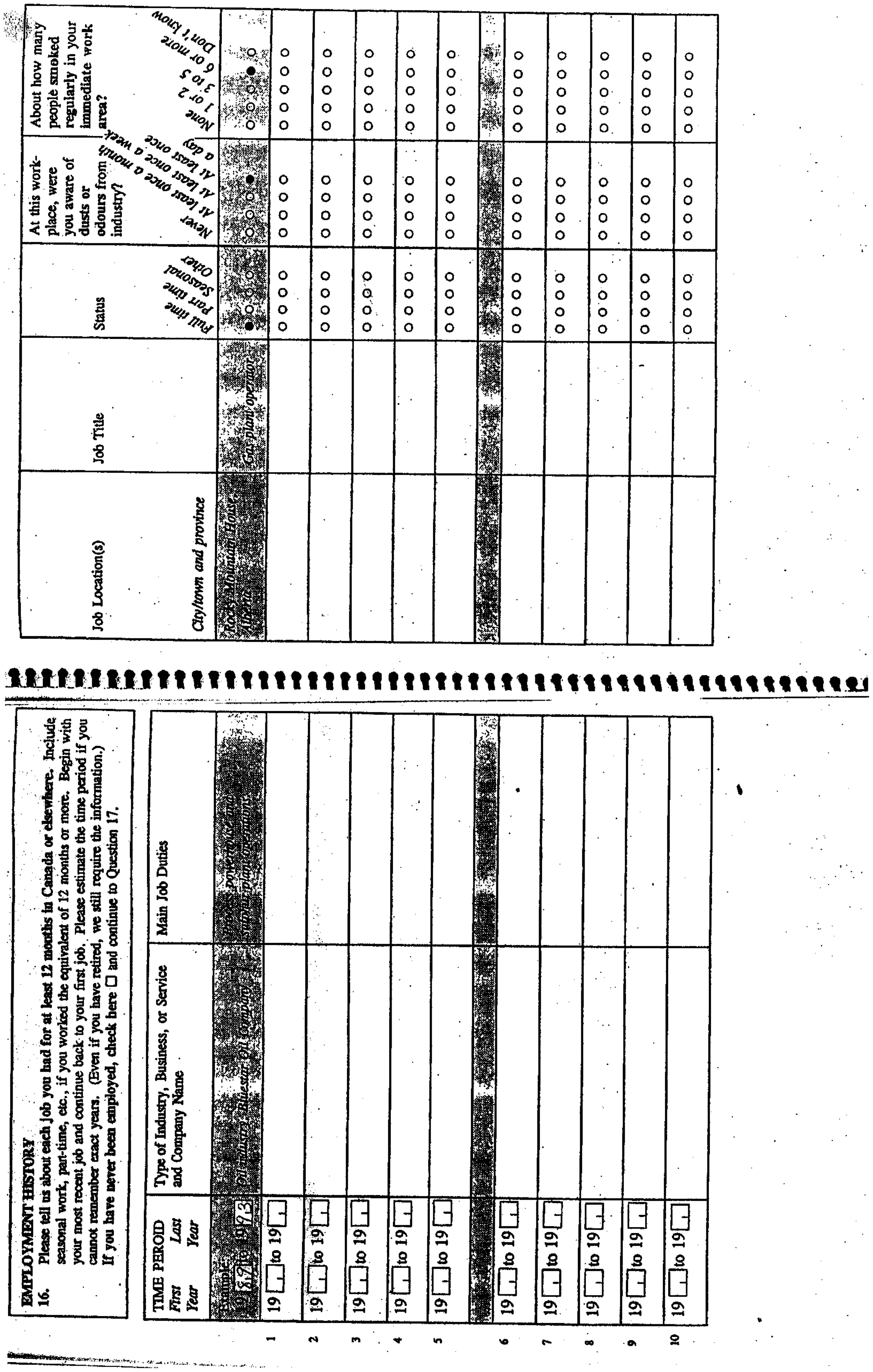
these two provinces were based upon the number of individuals ascertained after telephone contact. For Alberta, of the numbers called, 4% were not in service or were businesses, there was a communication barrier in 4%, and no one could be reached for11%. Of those households contacted, 91% agreed to a census of residents, and 90% of the eligible individuals agreed to be sent a questionnaire. For Newfoundland, exact contact and eligibility rates were not available; however, study personnel estimated that 85% of phone numbers were reached. Cooperation levels were similar to those in Alberta.

3.3 Questionnaire Data

Data collected in the NECSS questionnaire that were of interest for our study of the risk of NHL associated with occupational exposure to power frequency magnetic fields (MF) included: complete occupational history including all jobs held for at least twelve months (including information on job title, main job duties, type of industry, business or service, and company name, location, work status, and first and last calendar year for each job); self-reported work with various substances (including benzene, pesticides, herbicides, and radiation sources) at home and at work and the number of years of work with each; average annual family income for the past five years; smoking history; educational history; and complete residential history including method of home heating.

Subjects were asked to provide information about each job or occupation held for at least twelve months either in Canada or elsewhere, indicating whether the job was seasonal work, part-time work, etc,. This information was to be entered into the table shown in Figure 3.1. Subjects were asked to begin with their most recent job and

Figure 3.1. Reproduction of the employment history table in the NECSS questionnaire



EMPLOYMENT HISTORY

16. Please tell us about each job you had for at least 12 months in Canada or elsewhere. Include seasonal work, part-time, etc., if you worked the equivalent of 12 months or more. Begin with your most recent job and continue back to your first job. Please estimate the time period if you cannot remember exact years. (Even if you have retired, we still require the information.) If you have never been employed, check here ☐ and continue to Question 17.

	TIME PEROID First Year / Last Year	Type of Industry, Business, or Service and Company Name	Main Job Duties	Job Location(s) City/town and province	Job Title	Status (Full time / Part time / Seasonal / Other)	At this workplace, were you aware of dusts or odours from industry? (Never / At least once a month / At least once a week / At least once a day)	About how many people smoked regularly in your immediate work area? (None / 1 or 2 / 3 to 5 / 6 or more / Don't know)
1	19__ to 19__					o o o o	o o o o	o o o o o
2	19__ to 19__					o o o o	o o o o	o o o o o
3	19__ to 19__					o o o o	o o o o	o o o o o
4	19__ to 19__					o o o o	o o o o	o o o o o
5	19__ to 19__					o o o o	o o o o	o o o o o
6	19__ to 19__					o o o o	o o o o	o o o o o
7	19__ to 19__					o o o o	o o o o	o o o o o
8	19__ to 19__					o o o o	o o o o	o o o o o
9	19__ to 19__					o o o o	o o o o	o o o o o
10	19__ to 19__					o o o o	o o o o	o o o o o

continue back to the first job with an estimation of the time period if the exact years could not be remembered. They were asked to provide this information even if currently retired. In addition, subjects were asked to check a box if they had never been employed.

With respect to work with various substances, all subjects (whether they had ever been employed or not) were asked to complete a second table indicating whether they had ever worked with a number of listed items for more than one year. The columns of the table included four check boxes ('never', 'don't know', 'at work', and 'at home'); and a box to indicate the number of years in total. Substances of interest for our study in this table included benzene, pesticides, herbicides, radiation sources, and welding.

The complete questionnaire (entitled "Canadian Study of Health and the Environment") is attached as Appendix 1.

3.4 Database Contents

Data for the approximately 26,000 cancer cases and 5,039 controls were entered into the database by members of Health Canada from the information provided to them by the provinces. Generally the data from the questionnaire were entered into the database directly from subject's completed responses without corrections. For each subject, a maximum of 14 occupations and 15 residences were entered; if more were listed in the questionnaire, the data entry process excluded those with the shortest length followed by those with the earliest date.

Health Canada provided the portion of this database necessary for our study in four separate files: a subject file, an occupational file, a residential file, and a formats

file. Data for all subjects coded as NHL cases and for all subjects coded as controls were included in these files. Subjects were identified by a subject identification variable that allowed linkage of the first three files. Cases and controls were identified by the dichotomous control variable (0 for cases and 1 for controls). Specific information regarding the NHL was provided in the histology and topography variables in the subject file.

The variables included in each of the subject, occupational, and residential files that were of interest in our study are listed in Tables A2.1, A2.2, and A2.3, respectively, of Appendix 2. A description of these variables and their coded values is also provided in these tables.

3.5 Coding of Histology and Topography for Non-Hodgkin's Lymphoma

The cancer cases in the case-control component of the NECSS were classified by histology and morphology; two variables were included in the database for coding of topography and morphology. The topography code numbers were used to record the site of origin of the neoplasm. The morphology code numbers were used to record the histologic type, grade, and behaviour of the tumor as diagnosed microscopically by a pathologist. A brief description of the coding systems used to classify histology and topography is provided in the literature review (section 2.1.1.3) as the information provided in these variables was important for our study in order to analyze NHL risk by histologic subtype and by the primary site of the NHL (nodal versus extranodal).

Histology and topography were coded at the provincial or local level. The cancer cases included in the NECSS were primarily classified using Version 2 of the ICD-O.[130 (p. 101)] However, a few NHL cases had histology codes from version 1 of the ICD-O. Data

for the topography variable for NHL cases from Ontario included codes ranging between 200 to 208, codes used in Chapter II of ICD-9 to code for malignant neoplasms of lymphatic and haematopoietic tissue (such as reticulosarcoma, lymphosarcoma, Burkitt's lymphoma, and mycoses fungoides). These codes, however, are not included as topography codes in the ICD-O.

CHAPTER 4
METHODS II: Thesis Study

Overview

The assessment of non-Hodgkin's lymphoma (NHL) risk associated with occupational magnetic field (MF) exposure in this thesis is based upon a secondary analysis of the case-control data collected within the National Enhanced Cancer Surveillance System (NECSS). In this chapter, the methods used in our study will be described, including the formation of the study population, exposure assessment, calculation of exposure metrics, data management, and statistical analysis.

4.1 Study Population

A total of 1,666 cases with NHL and 5,039 controls were included in the original data files provided by Health Canada. In order to create our study population, one control was selected for each NHL case, matching by sex and five-year age category. The age groupings for the matching were: <25, 25-<30, 30-<35, 35-<40, 40-<45, 45-<50, 50-<55, 55-<60, 60-<65, 65-<70, and 70+ years. The control matched to each case was chosen at random from the pool of eligible controls. The full control group was not used in our analysis to limit resources required for exposure assessment. Pair matching was done to achieve an equal sex and age distribution between cases and controls. Given that sex and age are significant predictors of NHL risk, this matching will optimize the precision of the results for a given total sample size. One case who was missing both age and age group data was excluded from the study population. The remaining 1,665 NHL cases were matched to 1,665 controls.

After the pair matching was carried out, a further 63 subjects (41 cases and 22 controls) were excluded from the study population for the following four reasons:

1) Twelve subjects (11 cases and 1 control) were excluded due to discrepancies between either the coded value for the cancer site (NHL) or the coded value for the control status (control) and the coded values for the histology and/or topography:

   2 cases coded as Hodgkin's disease;

   1 case coded as chronic lymphocytic leukemia;

   8 cases coded as hairy cell leukemia; and

   1 control coded as chordoma in the pelvic bones, sacrum, coccyx, and associated joints.

2) Eight cases of hairy cell leukemia were originally included in the NHL cases collected by Ontario because, in Ontario, the initial classification of tumors used the ICD-9 classification. In that system, hairy cell leukemia is classified as a NHL (coded as 202.4 for leukaemic reticuloendotheliosis). However, in both versions of the ICD-O, hairy cell leukemia is classified as a leukemia. Although in many modern classification systems hairy cell leukemia is considered to be a NHL,[131] it was decided to exclude these cases to maintain consistency with what was done in other provinces.

3) Fifteen subjects (11 cases, 4 controls) were excluded because one or more jobs in their employment history could not be assessed for MF exposure due to insufficient information provided regarding the job in the occupational file. The jobs that could not be assessed for MF exposure included observations in the occupational file with data for the start and end years but no descriptive information whatsoever or observations in the occupational file where the only description information available

were terms such as: 'self employed', 'worked for parents', 'military-classified', 'RCMP-confidential', 'hydro', 'Goodyear Canada', 'different jobs', 'motor wheel', or 'forman ?' (*sic*).

4) Thirty-two subjects (17 cases, 15 controls) were excluded because it was indicated in the subject file that the subject had been employed yet there were no job data available for these subjects in the occupational file. A further four subjects (2 cases, 2 controls) for whom it was indicated in the subject file that they had been employed were excluded because the only job data available for these subjects in the occupational file were either 'retirement' or 'disabled due to industrial accident'.

4.1.1 Study Subgroups

The study population was divided into subgroups based on histology and topography. We created these subgroups because NHL is a heterogeneous disease and we believed that these groupings may have represented more homogeneous diseases in terms of etiology.

4.1.1.1 Subgroups by Histology

Non-Hodgkin's lymphoma can be subdivided into several histologic subtypes. Two major classification schemes in use are the Working Formulation for Clinical Usage[17] and the Revised European-American Classification of Lymphoid Neoplasms (REAL)[19] as described in section 2.1.1.1 of this thesis. Subgroup analyses were carried out in our study by histologic subtype of NHL, as classified by these two systems.

Firstly, for the purposes of our analyses, we subdivided the NHL cases according to the Working Formulation for Clinical Usage[17] into three groups: low-, intermediate-, and high-grade. These subdivisions were used because: a) these subgroups have been

used in earlier studies of NHL and MF; and b) the ICD-O coding system is most easily translated to this classification scheme. However, the Working Formulation, while useful to determine prognosis and make treatment decisions, does not recognize distinct clinicopathologic entities. Thus, it is less useful when trying to establish disease etiology.

Secondly, we subdivided the NHL cases according to the REAL[19] classification system for lymphoid malignances into: follicular lymphoma, diffuse large cell lymphoma, and small lymphocytic lymphoma. These subdivisions were used because: a) according to Aster and Kumar,[9 (p. 651)] "only four entities constitute the majority of lymphoid lymphomas and leukemias in adults: follicular lymphoma, large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and multiple myeloma"; and b) it was believed that these may represent distinct diseases with distinct etiologies.

We translated the ICD-O version 1 morphology codes to the Working Formulation using the algorithm of Percy *et al.*[132] We translated the ICD-O version 2 codes to the Working Formulation using the information provided in Table 2 of the "Instructions for Use of ICD-O, Second Edition".[32 (p. xxxiii)] We then used the Working Formulation type assigned to each case to assign a disease entity in the REAL system to that case. The NHL cases that we had classified as either type B, C, or D in the Working Formulation were included in the follicular subgroup, those classified as G or H were included in the diffuse large cell subgroup, and those classified as A were included in the small lymphocytic subgroup. The exception to this rule was that cases with ICD-O morphology codes where the 6th digit indicated the cell of origin to be a T-cell were not translated to the REAL system because the entities of interest in this system (i.e., the follicular, diffuse large cell, and small lymphocytic lymphomas) are B-cell lymphomas.

As reported by Herrington,[133] it was shown in a study published in 1996 that the Working Formulation entities follicular lymphoma, diffuse large cell lymphoma, and small lymphocytic lymphoma translate well to the REAL system. According to Aster and Kumar,[9] the lymphomas categorized as B, C, and D in the Working Formulation are approximately the equivalent of the follicular lymphomas of the REAL system; the lymphomas categorized as G and H are the equivalent of the diffuse large B-cell lymphomas along with the less common T-cell anaplastic large cell lymphoma; and the lymphomas categorized as A are the equivalent of chronic lymphocytic leukemia/small lymphocytic lymphoma along with the less common lymphoplasmacytic lymphoma and marginal zone lymphoma. However, it should be recognized that, despite the creation of these subgroups, there still is some overlap with other entities included in the REAL system as the ICD-O coding does not allow complete identification of these diseases.

Table 4.1 provides the specific ICD/O codes, the number of cases, and the translation of these codes to the Working Formulation and the REAL system used in our study.

4.1.1.2 Subgroups by Topography

Non-Hodgkin's lymphoma can also be classified according to the primary site of the tumor. According to the ICD-O Version 3, lymphomas that arise in lymph nodes are termed 'nodal' lymphomas while lymphomas that arise from other lymphatic tissue, such as tonsils, spleen, Weldeyer's ring, or thymus or from lymphatic tissue in organs, are termed are termed 'extranodal' lymphomas.[4 (p. 26)] Lymphatic malignancies that arise in the bone marrow are classified as leukemias. This classification was considered because: a) the reported increase in incidence of NHL has been greater for the extranodal lymphomas; b) there is evidence that extranodal lymphomas may have a

Table 4.1 Translation of the ICD-O morphology codes to the Working Formulation (WF) and the Revised European-American Classification of Lymphoid Malignancies (REAL) for the 1,624 non-Hodgkin's lymphoma cases, NECSS, Canada 1994-1997

ICD-O code	Version	Number of cases	Subtype by WF	Subgroup by WF	Subgroup by REAL
9590	Both	296	Unclassifiable*	-	-
9591	Both	35	Unclassifiable	-	-
9595	Second	8	Unclassifiable	-	-
9600	First	3	J	High	-
9610	First	3	Unclassifiable	-	-
9611	First	4	A	Low	Small lymphocytic
9612	First	22	H	High	Diffuse large cell
9613	First	27	F	Intermediate	-
9614	First	2	F	Intermediate	-
9620	First	64	A	Low	Small lymphocytic
9621	First	9	E	Intermediate	-
9630	First	2	E	Intermediate	-
9640	First	127	G	Intermediate	Diffuse large cell
9670	Second	94	A	Low	Small lymphocytic
9671	Second	9	A	Low	Small lymphocytic
9672	Second	29	E	Intermediate	-
9673	Second	21	E	Intermediate	-
9674	Second	1	E	Intermediate	-
9675	Second	57	F	Intermediate	-
9680	Second	183	G	Intermediate	Diffuse large cell
9681	Second	12	G	Intermediate	Diffuse large cell
9682	Second	38	G	Intermediate	Diffuse large cell
9683	Second	1	G	Intermediate	Diffuse large cell
9684/3	Second	33	H	High	Diffuse large cell
9684/35	Second	2	H	High	-
9685	Second	4	I	High	-
9685/35	Second	1	I	High	-
9686	Second	10	J	High	-
9687	Second	2	J	High	-
9690	Both	39	Unclassifiable	-	-
9691	Both	145	C	Low	Follicular
9692	Both	2	B	Low	Follicular
9693	Both	1	B	Low	Follicular
9694	Both	1	B	Low	Follicular
9695	Both	173	B	Low	Follicular
9696	Both	6	B	Low	Follicular
9698	Both	66	D	Intermediate	Follicular
9700	Both	30	Miscellaneous**	-	-
9702	Second	2	Miscellaneous	-	-
9704	Second	3	Miscellaneous	-	-
9706	Second	2	Miscellaneous	-	-
9707	Second	3	Miscellaneous	-	-
9709	Second	11	Miscellaneous	-	-
9711	Second	7	Miscellaneous	-	-
9713	Second	2	Miscellaneous	-	-
9714	Second	14	Miscellaneous	-	-
9715	Neither	6		-	-
9720	Both	1	Miscellaneous	-	-
9723	Second	5	Miscellaneous	-	-
9750	First	3	J	-	-
9760	Second	1	Miscellaneous	-	-
9761	Second	2	Miscellaneous	-	-

* Unclassifiable- ICD-O code too non-specific to allow further classification.
** Miscellaneous- Specific NHL subtypes not included in the Working Formulation.

better prognosis[32] (p. xxxv); and c) there is evidence to suggest that extranodal lymphomas arise from lymphoid cells of the MALT system, and that these lymphocytes have different properties from those of the lymph nodes.[73]

The cases of NHL in our study were classified as nodal or extranodal according to the above definitions. Cases with topography indicated as bone marrow or blood were not classified by nodal versus extranodal status. In addition, cases were not classified by nodal status where the topography codes were too nonspecific to allow this type of classification. For example, cases with topographies of 'mediastinum', 'retroperitoneum', or 'thorax NOS' were not classified as it was unclear whether these arose in lymph nodes or in other tissues in these locations. Further, those cases for whom ICD-9 codes rather than ICD-O topography codes were provided for the topography variable (i.e., the Ontario cases) were not classified by nodal versus extranodal status.

Table 4.2 provides the specific values for the topography codes, the system the code is from, the number of NHL cases with these codes, and the classification of these codes as either nodal, extranodal, or unclassified.

4.2 Exposure Assessment

Exposure to power frequency magnetic fields (MF) was assessed for each job held by all subjects in our study. These exposure assessments for each job were categorized as follows:

- 1 = average MF flux density less than 0.3 microTesla (μT);
- 2 = average MF flux density between 0.3 and 0.6 μT;
- 3 = average MF flux density equal to or greater than 0.6 μT;
- 0 = insufficient information to estimate exposure.

Table 4.2 Classification of the topography codes as nodal, extranodal, or unclassifiable for the 1,624 non-Hodgkin's lymphoma cases, NECSS, Canada 1994-1997

Topography code	Coding system	Number of cases	Topography subgroup
200.0	ICD-9	201	Unclassifiable- ICD9 code
200.1	ICD-9	101	Unclassifiable- ICD9 code
200.2	ICD-9	5	Unclassifiable- ICD9 code
200.8	ICD-9	61	Unclassifiable- ICD9 code
202.0	ICD-9	152	Unclassifiable- ICD9 code
202.1	ICD-9	7	Unclassifiable- ICD9 code
202.8	ICD-9	89	Unclassifiable- ICD9 code
C00.3	ICD-O/2	1	Extranodal
C01.9	ICD-O/2	3	Extranodal
C02.4	ICD-O/2	1	Extranodal
C03.1	ICD-O/2	1	Extranodal
C05.1	ICD-O/2	1	Extranodal
C07.9	ICD-O/2	11	Extranodal
C08.0	ICD-O/2	5	Extranodal
C08.9	ICD-O/2	1	Extranodal
C09.9	ICD-O/2	12	Extranodal
C11.2	ICD-O/2	1	Extranodal
C11.3	ICD-O/2	1	Extranodal
C11.9	ICD-O/2	3	Extranodal
C14.0	ICD-O/2	1	Extranodal
C14.2	ICD-O/2	1	Extranodal
C15.3	ICD-O/2	1	Extranodal
C16.0	ICD-O/2	1	Extranodal
C16.1	ICD-O/2	2	Extranodal
C16.2	ICD-O/2	6	Extranodal
C16.3	ICD-O/2	11	Extranodal
C16.5	ICD-O/2	3	Extranodal
C16.6	ICD-O/2	2	Extranodal
C16.8	ICD-O/2	1	Extranodal
C16.9	ICD-O/2	27	Extranodal
C17.0	ICD-O/2	2	Extranodal
C17.1	ICD-O/2	1	Extranodal
C17.2	ICD-O/2	1	Extranodal
C17.8	ICD-O/2	1	Extranodal
C17.9	ICD-O/2	10	Extranodal
C18.0	ICD-O/2	6	Extranodal
C18.8	ICD-O/2	2	Extranodal
C22.0	ICD-O/2	3	Extranodal
C23.9	ICD-O/2	2	Extranodal
C25.0	ICD-O/2	1	Extranodal
C25.8	ICD-O/2	1	Extranodal
C25.9	ICD-O/2	2	Extranodal
C26.0	ICD-O/2	1	Extranodal
C30.0	ICD-O/2	2	Extranodal
C30.1	ICD-O/2	1	Extranodal
C34.0	ICD-O/2	3	Extranodal
C34.1	ICD-O/2	2	Extranodal
C34.2	ICD-O/2	1	Extranodal
C34.3	ICD-O/2	2	Extranodal
C34.8	ICD-O/2	1	Extranodal

Table 4.2 (con't.) Classification of the topography codes as nodal, extranodal, or unclassifiable for the 1,624 non-Hodgkin's lymphoma cases, NECSS, Canada 1994-1997

Topography code	Coding system	Number of cases	Topography subgroup
C34.9	ICD-O/2	3	Extranodal
C38.1	ICD-O/2	4	Unclassifiable-code not specific
C38.2	ICD-O/2	1	Unclassifiable-code not specific
C38.3	ICD-O/2	9	Unclassifiable-code not specific
C38.4	ICD-O/2	1	Extranodal
C40.0	ICD-O/2	3	Extranodal
C40.2	ICD-O/2	6	Extranodal
C40.3	ICD-O/2	1	Extranodal
C41.1	ICD-O/2	1	Extranodal
C41.2	ICD-O/2	5	Extranodal
C41.3	ICD-O/2	1	Extranodal
C41.4	ICD-O/2	2	Extranodal
C42.0	ICD-O/2	2	Unclassifiable- code for blood
C42.1	ICD-O/2	47	Unclassifiable- code for bone marrow
C42.2	ICD-O/2	8	Extranodal
C44.1	ICD-O/2	2	Extranodal
C44.3	ICD-O/2	6	Extranodal
C44.4	ICD-O/2	3	Extranodal
C44.5	ICD-O/2	12	Extranodal
C44.6	ICD-O/2	4	Extranodal
C44.7	ICD-O/2	8	Extranodal
C44.8	ICD-O/2	3	Extranodal
C44.9	ICD-O/2	15	Extranodal
C48.0	ICD-O/2	3	Unclassifiable- code not specific
C48.1	ICD-O/2	4	Extranodal
C49.0	ICD-O/2	3	Extranodal
C49.1	ICD-O/2	5	Extranodal
C49.2	ICD-O/2	5	Extranodal
C49.3	ICD-O/2	7	Extranodal
C49.4	ICD-O/2	1	Extranodal
C49.6	ICD-O/2	1	Extranodal
C49.9	ICD-O/2	1	Extranodal
C50.8	ICD-O/2	1	Extranodal
C50.9	ICD-O/2	4	Extranodal
C57.1	ICD-O/2	1	Extranodal
C61.9	ICD-O/2	2	Extranodal
C62.1	ICD-O/2	2	Extranodal
C62.9	ICD-O/2	11	Extranodal
C64.9	ICD-O/2	1	Extranodal
C69.0	ICD-O/2	6	Extranodal
C69.5	ICD-O/2	2	Extranodal
C69.6	ICD-O/2	3	Extranodal
C69.9	ICD-O/2	2	Extranodal
C71.0	ICD-O/2	1	Extranodal
C71.1	ICD-O/2	5	Extranodal
C71.2	ICD-O/2	1	Extranodal
C71.3	ICD-O/2	3	Extranodal
C71.4	ICD-O/2	1	Extranodal
C71.8	ICD-O/2	1	Extranodal
C71.9	ICD-O/2	4	Extranodal

Table 4.2 (con't.) Classification of the topography codes as nodal, extranodal, or unclassifiable for the 1,624 non-Hodgkin's lymphoma, NECSS, Canada 1994-1997

Topography code	Coding system	Number of cases	Topography subgroup
C73.9	ICD-O/2	8	Extranodal
C76.0	ICD-O/2	1	Unclassifiable-code not specific
C76.1	ICD-O/2	1	Unclassifiable-code not specific
C76.2	ICD-O/2	7	Unclassifiable-code not specific
C76.3	ICD-O/2	1	Unclassifiable-code not specific
C76.5	ICD-O/2	2	Unclassifiable-code not specific
C77.0	ICD-O/2	199	Nodal
C77.1	ICD-O/2	21	Nodal
C77.2	ICD-O/2	67	Nodal
C77.3	ICD-O/2	50	Nodal
C77.4	ICD-O/2	69	Nodal
C77.5	ICD-O/2	5	Nodal
C77.8	ICD-O/2	45	Nodal
C77.9	ICD-O/2	161	Nodal
C80.9	ICD-O/2	1	Extranodal

The lower cutpoint of 0.3 μT was chosen to represent background exposure received at home or other non-work situations, whereas those in the upper two categories were chosen to represent exposure levels greater than background. As described by Villeneuve *et al*[134], the cutpoint of 0.3 μT corresponded to the 82nd percentile for exposures in the home in a Canadian study of residential MF exposures and childhood leukemia.[135] The upper cutpoint of 0.6 μT was chosen as it was double the lower cutpoint.

The MF exposure assessments for each job were carried out by Dr. D. Agnew, a physicist with expertise in the area of electromagnetic field exposure associated with electricity. He used methodology similar to that used in an earlier study by Villeneuve *et al*[134] of the risk of brain cancer associated with occupational exposure to MF in the NECSS case-control population. Occupational exposure to MF depends upon several factors in addition to the obvious job title or type. These factors include work location, specific environments and exposures, and type of business. Thus, Dr. Agnew carried out the MF exposure assessments on a job-by-job basis. He did this using all the information included in the NECSS occupational data file for the variables representing 'Type of Industry, Business, or Service and Company Name', 'Main Job Duties', and 'Job Title', in conjunction with his knowledge and resources in the area of electromagnetic fields. He has collected extensive data on occupational measurements of MF exposure from many sources, including: literature publications[2 136 137 138 139]; the United States government Department of Energy's 'Rapid' Program and the Electrical Power Research Institute[140] databases; and personal communications with others in the field. These data are related to either specific occupations or specific industries. In addition, he has collected measurement data of MF emitted from various sources.[139] These

measurements were used to estimate occupational exposures through knowledge of exposure to known sources in a given occupation (e.g., hairdryers and electric clippers in the hair stylist occupation) when specific occupational exposure measures for that occupation or industry were not available. Magnetic field exposure to many occupational factors may have changed over the last 50 years, possibly having been reduced through enhanced safety protocols and improved manufacturing processes, or, alternatively, having been increased through increased use of electrical equipment and equipment with higher currents. However, the occupational exposure assessments were not adjusted for possible effects due to the era in which the job was held because there is little or no information available on the change of MF with time for the various occupations. Because knowledge of case-control status might have resulted in bias in assigning exposure, the exposure assessments were carried out with the assessor blinded to each subject's case-control status.

In addition, Dr. Agnew assessed each job for exposure to ionizing radiation using the same job information (i.e., job title, job duties, and type of industry and company name) used in his assessment of MF exposure. Each job was assigned a value of 1 if the annual exposure was considered likely to exceed 1 milliSievert (mSv) and 0 if the annual exposure was expected to be less than 1 mSv.

The Surveillance and Risk Assessment Division in Health Canada's Centre for Chronic Disease Prevention and Control provided funding for these expert MF and ionizing radiation exposure assessments.

4.3 Exposure Indices

The primary exposure index of interest was the cumulative exposure to power frequency MF above background levels occurring in the occupational setting from age 18 to two years before the interview date. In addition, other exposure indices were considered in secondary exploratory analyses.

4.3.1 Primary Exposure Index

The cumulative occupational MF exposure index for each subject was calculated by taking into account the MF exposure intensity, the duration of employment, and the status of the job (full-time, part-time, etc.) for all jobs held by a subject. Mathematically, it was calculated by summing the status-weighted exposure intensity over the number of years each job was held and over all jobs as described by the formula:

$$Cumulative\ MF = \sum_{jobs} \sum_{years} MF\ exposure\ intensity_i\ x\ job\ status_i$$

This continuous cumulative index was determined for each subject in order that the subjects could be rank ordered in terms of total cumulative exposure to MF.

The MF exposure intensity value was assigned to each job based upon the original expert assessment of the MF exposure of each job. The MF exposure intensity was assigned numerical values of 0, 1, and 2 for the categories background (less than 0.3 μT), medium (0.3 μT to less than 0.6 μT), or high exposures (0.6 μT and greater), respectively. These values were chosen in order that the background level was assigned the numerical value of zero, and that the numerical distance between categories was equal. By doing so, the background level of exposure at work was treated the same as exposures experienced in the non-work setting. In addition, the values of 1 and 2 were

proportional to the cut-points of 0.3 μT and 0.6 μT, which was necessary in order that the cumulative exposure index made sense.

The value for the status variable was assigned based upon the presumed proportion of full-time hours worked in the job: full-time jobs were assigned the value 1; full-time seasonal or part-time jobs the value of 0.5; and part-time seasonal jobs the value of 0.25.

Exposures occurring during the two years prior to the interview date were ignored because it was considered that these exposures were not relevant to the causation of disease as they would have occurred during the induction or latent periods. We have referred to this period as the lag period. The jobs that were held by subjects before age 18 were not included, as is the standard practice in occupational epidemiology.

The continuous cumulative exposure index was divided into four categories of exposure (background, low, medium, and high). All subjects with values of zero were included in the background level category while those with values above zero were divided into three groups: low, medium, and high exposure. The categorization of low, medium, and high was based on the tertile cutoff points for the distribution of the continuous cumulative exposure index in both cases and controls with values greater than zero for this index. The four categories of cumulative exposure were thus defined as background (values of zero), greater than 0 to less than the first tertile (low), greater than or equal to the first tertile to less than the second tertile (medium), and greater than or equal to the second tertile (high). The values of the first and second tertiles were 6.0 and 20.0, respectively; the median values of the continuous index for each of the four categories were 0, 3, 11, and 32.

4.3.2 Other Exposure Indices

Other exposure indices were created for use in secondary exploratory analyses for two purposes. Firstly, it is unclear what measures of MF exposure or 'dose' are relevant in cancer risk assessment because the biophysical mechanism of action of MF in living tissues is unknown. Secondly, other exposure indices have been used in other studies; thus the inclusion of other indices in our study would allow comparisons with these other studies. The other indices used in our exploratory analyses included:

- cumulative exposure with a five-year lag period;
- cumulative exposure with no lag period;
- cumulative exposure with a two-year lag period but including jobs held before age 18;
- cumulative exposure with a two-year lag period in ten year time windows, (i.e., cumulative exposure in the time period 3 to12 years prior to the interview date, cumulative exposure in the time period 13 to 22 years prior to the interview date, etc.);
- average exposure intensity based upon the exposure category of the job held the longest in the time period from age 18 to two years before the interview date;
- highest intensity of exposure based upon the exposure category of the job with the highest category of exposure ever held in the time period from age 18 to two years before the interview date; and
- number of years worked (i.e., duration of exposure) in jobs with exposure assessed as having an average magnetic flux density equal to or greater than 0.3 μT (i.e., exposure above background levels) in the time period from age 18 to two years before the interview date.

The secondary indices for cumulative exposure were categorized as for the primary index. For the indices with different lag periods, the same cutpoints (6.0 and 20.0) as for the primary cumulative exposure were used. For the cumulative exposure indices in ten-year time windows, cutpoints were created based on the distribution of all values above zero in all ten-year time windows for both cases and controls. These cutpoints were 5.0 and 10.0; the median values for each of the four categories were 0, 2.5, 7.5, and 10.0. The index 'duration of exposure in jobs with MF exposure above background' was categorized similarly to the cumulative exposure indices. The reference category included those with no exposure above background, while the three categories of short, medium, and long duration were defined using as cutpoints the tertiles of the distribution of the number of years worked in jobs with MF exposure above background in cases and controls combined. These cutpoints were 5.5 and 17.5; the median values for each of the four categories were 0, 2.5, 8.5, and 26.5 years.

4.3.3 Derivation of Exposure Indices

In order to derive the exposure indices for each subject, a year-by-year MF exposure file was created, where observations were created for each year worked by a subject. The years were numbered starting from 0 at the interview year continuing backwards. For each job held from age 18 or older, an observation for each individual year of work in that job was created which included the subject identification variable, a job number variable, a year variable, an MF exposure intensity variable, a status variable, and an MF cumulative exposure variable. Values for the variables 'MF exposure intensity', 'job status', and 'MF cumulative exposure' for each year were derived as follows:

- The value for the exposure intensity variable was assigned based upon the MF exposure assessment for the job held during that year. The original values of 1, 2, and 3 for the MF exposure assessment were reassigned for the MF exposure intensity variable to 0, 1, and 2.
- The value for the status variable was assigned based on the job status reported for the job held for that year. Full-time jobs were assigned the value 1; full-time seasonal or part-time job the value of 0.5; and part-time seasonal jobs the value of 0.25.
- The MF cumulative exposure variable was derived as the product of the MF exposure intensity variable and the job status variable for the given job for the given year.

No observation was created for years where no job was held. Because background exposure in the occupational setting was considered the same as exposure in the non-work setting, it was not necessary to account for years that were not worked as they contributed no excess exposure above background to the cumulative exposure total.

In some instances, two jobs for a given subject had the start year for a job the same as the end year from an earlier job (e.g., job #1 1993 to 1996, job #2 1991 to 1993). In these cases, it was assumed that the subject had changed jobs midway through the year. Two observations were created with the same value for the year for the subject. When cumulative exposure or duration of years worked were calculated, the average of the two values of the appropriate variable for the two jobs for that year was used in the calculation.

From this file, the various exposure indices were calculated for each subject using all observations for the given subject. For the cumulative exposure indices, the

values for the cumulative exposure variable for all observations for a given subject with values for the year variable in the time window of interest were added together. The value for highest exposure in any job index was the maximum value of the MF intensity for the subject from any year before year 2. In order to determine the exposure intensity in the job held the longest, the duration of each job was calculated by summing the values of the status variable for each year for a given job (with years 0, 1, and 2 excluded). The value of the MF intensity variable for the job with the longest duration was assigned for this index; if there was a tie for the maximum duration between two or more jobs for a given subject, the maximum value of the MF intensity variable for these jobs was assigned. When there were two observations for a given year for subject, for calculations involving summation (i.e., cumulative exposure indices and job duration), the values for the variables involved were divided in half, such that values for each of the two jobs were attributed to half of the particular year.

In addition, the total number of full-time equivalent years worked for each subject was calculated from this file; this number was the sum of the values for the job status variable for all years for that subject. The total number of years worked included the two-year period prior to interview.

Specific examples of the derivation of these MF exposure indices are provided in Appendix 3.

4.4 Data Management

Overview

The database provided by Health Canada contained data for the 3,267 subjects (1,624 cases and 1,643 controls) in the study population and the 11,379 occupations

associated with these subjects. As our study was a secondary analysis of those data, specific data values could not be verified against the original records. There were some difficulties in analyzing the data, including missing data, some data entry errors, and some data inconsistencies, particularly with respect to job dates. Therefore, in order to proceed with our analyses, it was necessary to make some decisions regarding these data. In the case of the job year data, several options to resolve the difficulties were possible. For our primary analyses, we chose to exclude all subjects with missing or inconsistent job year data for any job held from age 18 or older, but assessed several of the other possible methods through various secondary sensitivity analyses. In order to carry out these sensitivity analyses, we created four populations we called secondary analytic populations. In addition, although the controls in our study were selected by a pair matching process, we chose to ignore the pairing in our primary analyses. In order to assess the effects of this choice, we also created a population based only upon the matched pairs. Further, it was necessary to derive new variables in order to: assign values to each subject for the various MF exposure indices and other potential risk factors; to categorize certain variables; and to resolve some other data inconsistencies.

In this section, we describe first the revisions we made to the original data and second the new variables we derived. Information in these two subsections is presented under subheadings for the given variable. Next, we outline the difficulties we encountered with the occupational job year data. Finally, we describe the different secondary analytic study populations created for the sensitivity analyses and for the analysis based on the matched pairs.

4.4.1 Data Revisions

4.4.1.1 Subject File

ICD-O Morphology and ICD-O Topography: Several cases had ICD-O codes for histology that are contained in the first version of ICD-O but not in the second version. These codes were translated from ICD-O version 1 when subgroups based upon NHL histology were defined.

A total of 299 of the cases had histology coded as 'Malignant lymphoma, Not Otherwise Specified' (9590/3). Schroeder and Savitz[123] included cases with this ICD-O code in the NHL subgroup in their analysis of lymphoma and multiple myeloma mortality among electric utility workers. Since we were advised by Dr. P. Sloan of Cancer Care Ontario that this code does not include Hodgkin's disease, these cases were also included in all analyses except for the subgroup analyses based on histology.

Topography codes for all cases from Ontario were actually ICD-9 codes. These codes could not be used to determine the primary site of the NHL. Consequently, these cases were not included in the subgroup analyses based upon topography.

Four NHL cases had the histology code 9970/3. This code is not included in either Version 1 or 2 of the ICD-O. The histology and topography codes for these cases were revised to 9590/3 and 202.8, respectively, as advised by Dr. Sloan of Cancer Care Ontario. These cases had, in fact, been coded incorrectly due to a temporary coding problem within the Ontario registry.

The fifth digit in the value for the histology code variable which codes for behaviour was 0 (benign) in one case, 7 in a second case, and 2 (in situ) in a third case. These numbers were considered to be data entry errors and were ignored, as all lymphomas are considered malignant.

In 48 cases, topography was coded C42.1 (for bone marrow) and in 2 cases C42.0 (for blood), while the morphology codes for these cases indicated a type of NHL. It was assumed that these were cases of NHL and the site of biopsy rather than the primary site of the neoplasm had been indicated in the topography code.

In nine cases, the topography code had an extra fifth character. This extra character was located after the decimal place. It was assumed that the last character was a data entry error and it was ignored. For example, in one case the value for the topography variable was C34.31; the topography code was assumed to be C34.3.

Reporting province: For two subjects, the value for the variable province was missing. On examining the data, it was clear that the province of origin was also indicated in the first two digits of the subject identification number (i.e., the first two characters of the subject identification variable were the same as the code used for the province identification variable). Thus, the values for the province identification variable for subjects with missing values for this variable were changed appropriately. For example, for the subject with the identification number '12 951934', the value for the province identification variable was changed from missing to 12 (Nova Scotia).

Year at interview: For one case, the year at interview was coded as 1977. As cases had been recruited over the period 1994 to 1997, we considered this value to be a data entry error and revised it to 1997. However, as the age variable had been derived from the date of birth and the date of interview variables in the original Health Canada file, it was likely that the age and age group variables were also incorrect for this subject. While the date of birth was not available in our secondary analysis data file, the data available for this subject for the job history, which included data for three jobs held over the period 1958 through to 1997, and for the age (38 years) were not

compatible. Therefore, the value for age was changed from 38 to 58, and the value for the five-year age group category variables was changed appropriately.

Never been employed: The variable 'never been employed' was coded yes for subjects who indicated that they had never been employed and no for those who went on to fill in the occupational section of the questionnaire. The value for this variable was changed from no to yes (i.e., never been employed) for two subjects whose employment histories included the single observation of housewife. The occupation housewife was not considered formal work when the number of years worked variables was computed.

4.4.1.2 Occupational File

Job title, type of industry and company name, and main job duties: There were several observations within the occupational file where the information available indicated situations other than formal occupational employment, such as retirement, school, disability, unemployment, and housewife. These observations were deleted from the file. In order to identify these occupations, we manually reviewed the information available in the job title, job type, and job duties variables. In addition, we carried out an electronic search for the character string 'retire' to complement the manual review. While occupations listed as 'housewife', 'homemaker in own home', and 'student' were not considered formal employment and were deleted, occupations described specifically as 'farmwife', 'graduate student', 'internship', and 'nursing student in a hospital' were considered employment and were not deleted. In total, 209 occupations associated with 182 subjects were deleted from the occupational file.

Job start year and job end year: For four subjects (3 cases, 1 control), the start year of one of the listed jobs was much earlier than the date of interview minus the

age at interview (i.e., the calculated year of birth). Although it is possible that the age at interview was incorrect rather than the job start year, this did not appear to be the case from the other available occupational data. Thus, we changed the values for these job years to missing.

For twelve subjects, the year of interview was one year earlier than the end year of the most recent one or two jobs. For these subjects, the end year of these jobs were changed to that of the year of the interview.

The changes made are summarized in Table 4.3.

Table 4.3 Subjects with revisions made to job end year

Case/ control status	Age	Year at interview	Job #	Original job start year	Original job end year	Revised job start year	Revised job end year
Four subjects with job start earlier than calculated year of birth							
Case	51	1995	1	1907	1949	Missing	-
Case	42	1996	2	1926	1978	Missing	-
Case	48	1996	7	1934	1965	Missing	-
Control	61	1997	1	1905	1997	Missing	-
Twelve subjects with interview year one year earlier than job end year for most recent job(s)							
Case	62	1994	1	1968	1995	-	1994
Case	32	1995	1	1986	1996	-	1995
Case	36	1995	1	1993	1996	-	1995
Case	56	1995	1	1957	1996	-	1995
Case	32	1996	1	1986	1997	-	1996
Case	73	1996	1	1957	1997	-	1996
Case	53	1995	1	1968	1996	-	1995
Control	48	1996	1	1993	1997	-	1996
Control	42	1996	1	1993	1997	-	1996
			2	1994	1997		1996
Control	49	1996	1	1974	1997	-	1996
Control	71	1996	1	1987	1997	-	1996
Control	59	1995	1	1954	1996	-	1995

4.4.2 Derived Variables

The new variables we derived from the variables included in original files are described below. These variables, together with their title and coded values, are listed in Tables A2.4 and A2.5 of Appendix 2.

4.4.2.1 Subject File

Pair indicator: A variable was created to identify the matched pairs for use in analyses retaining the pairing.

Five-year age group: Age was 75 years for 39 subjects and 76 years for 3 subjects. However, within the NECSS data, the five-year age group categories ranged to a maximum of 70-74. Therefore, the highest age category was redefined to include the subjects aged 75 and 76. This change was made because the age matching for our secondary analysis was carried out using 70+ as the final age category and because there were a relatively small number of subjects over 74.

Education: Subjects were asked to provide the highest grade (or year) of high school or elementary school completed followed by the number of years of post-secondary school. In the NECSS database there were two variables available concerning education: total number of years of education (range 1-37); and highest grade in secondary/elementary school (range 0-13). For our analysis, education was dichotomized based upon highest grade attained: 'less than grade 12' or 'grade 12 and higher', (i.e., whether graduated high school).

Cigarette pack-years: The continuous variable indicating the number of pack-years in the subject's smoking history was categorized into four groups for our analyses. The cutpoints were defined based upon the tertiles of distribution of the continuous values of cases and controls who smoked. The categories were as follows: none, 1 to 9,

10 to 23, and greater than 23 pack-years. The median values of each of these categories were 0, 4, 16, and 35 pack-years.

Work with benzene, pesticides, herbicides, and pesticides or herbicides: Information on work with benzene, pesticides, and herbicides was present for both home and work settings. As we were interested in exposures due to work with these substances occurring in any setting, we created three new variables, one for each of benzene, pesticides, and herbicides, to identify subjects who had reported work with the particular substance at either home or work. These variables were named 'work with *the substance*' and were coded yes if either of the original variables for the particular substance related to work at home or work had been coded as yes, and as no otherwise.

In addition, we created a fourth variable named 'work with either pesticides or herbicides' to identify subjects who reported that they had worked with either pesticides or herbicides at either home or work. According to the scientific literature, herbicides are a sub-category of pesticides.[141] As such, the inclusion of separate items for pesticides and herbicides in the questionnaire could be questioned. However, since some people in the general public regard these as distinct chemical families (targeting live pests and plants respectively), failure to request information about both categories may have led to under-reporting of use. Therefore, we chose to combine self-reported work with pesticides and herbicides to capture work with all types of pesticides. The variable was coded as yes if any of the original variables for work with pesticides or herbicides at home or at work had been coded as yes, and as no otherwise.

Number of years worked from age 18: The number of full-time equivalent years worked from age 18 was calculated for each subject by summing together the

proportion of full-time hours worked each year (measured by the derived job status variable) from the year-by-year MF exposure file (see section 4.3 'Exposure Indices'). No lag period was used. This number of years worked was then categorized into four groups. The cutpoints were based on the distribution of the number of years worked among cases and controls in whom this number was greater than zero. These categories included none, 0.5 to less than 19, 19 to less than 33.5, and 33.5 to 58 years; the median values of these categories were 0, 11, 26, and 40 years.

Exposure to electric heat as the primary method of home heating: A variable was created to identify subjects who had indicated that a primary method of home heating had been electrical in any residence he/she had lived in for more than one year. This variable was coded 1 if any of the observations in the residential file for the subject had been coded yes for the electric home heat variable.

Expert-assessed ionizing radiation occupational exposure greater than 1 mSv: A variable was created to identify subjects who had held any job assessed by Dr. Agnew as having an annual exposure to ionizing radiation of more than 1 mSv. This variable was coded 1 if any of the observations in the occupational file for the subject had been coded 1 for the exposure to ionizing radiation variable.

4.4.2.2 Occupational File

Job status: We derived a variable named 'job status' from the original five variables regarding job status for each job included in the occupational file. These original variables were coded as 1 for yes and 0 for no for each of full-time status, part-time status, full-time seasonal status, part-time seasonal status, or other status. There was no information available to determine what was meant by the status 'other', although we believed that this likely indicated a work situation other than full-time

(perhaps casual, contract, or volunteer work). The new job status variable was created to reflect the proportion of full-time hours worked in the job, with the value 1 assigned to full-time jobs; the value 0.5 assigned to part-time and full-time seasonal jobs and to jobs with the status of 'other'; and the value 0.25 assigned to part-time-seasonal jobs.

However, difficulties in assigning values to the job status variable for each job were encountered. In 205 of the 11,170 jobs, the values for all five of the original variables regarding job status were either no or missing; while in a further 149 jobs more than one of these status variables were coded yes (e.g., a job was indicated to have had been both full-time and part-time). For the 205 jobs where none of the original status variables were coded yes, the average value of the derived job status variable for the jobs of the control subjects (0.91) was imputed. For jobs where more than one of the original five status variables was coded yes, the average of the assigned values for all the variables coded yes was taken. For example, if both the full-time and part-time original status variables were coded yes for a given job, then the derived job status variable for this job was assigned the value 0.75, the average of 1.0 and 0.5.

Imputed job start year and job end year: There were 202 jobs with missing values for the start and/or end year, while the remainder of the data for these jobs were relatively complete. Subjects with these missing dates were excluded from the primary analyses. In order to carry out a sensitivity analysis to explore the potential bias introduced by excluding these subjects, values for the start and end years for jobs with missing values for these variables were imputed according to the assumptions outlined below. These imputations were done without knowledge of the exposure assessment of the jobs or of case/control status of the subject so as not to create bias. The assumptions were made only if the data available (including job years provided and

information provided in the text describing the jobs) did not suggest otherwise. In some instances it was not possible to impute values since the other available data suggested that the assumptions were incorrect.

Imputation assumptions

- the subject worked continuously from age 18 to 65 or until date of interview for those less than 65 years of age;
- jobs were listed in order, from most recent to earliest, as indicated in the directions in the questionnaire;
- only one job was held at a time;
- the total working time was divided equally among all jobs with missing year data for a given subject;
- any job year information provided in the text describing the job title, type, or duties for jobs with missing year data was correct.

Imputations for start and/or end years were carried out for 170 jobs associated with 95 subjects (i.e., 1.5% of the total number of jobs associated with 2.9% of the total number of subjects). Imputation was not considered possible for 17 jobs associated with 11 subjects.

4.4.3 Difficulties with the File for Year-by-Year MF Exposure

As described in section 4.3, a year-by-year MF exposure file was created in order to calculate the exposure indices and number of years worked for individual subjects. However, some difficulties were encountered in the creation of this file because in some cases, more than one job was listed for a given year for a subject. In part, this was due to the fact that the start and end years between consecutive jobs were the same. For

example, a subject may have listed four jobs, with the start and end years for each job indicated to be 1960 to 1965, 1965 to 1970, 1970 to 1976, and 1976 to 1995; while another subject may have listed four jobs, with the start and end years for each job indicated to be 1960 to 1964, 1965 to 1969, 1970 to 1975, and 1976 to 1995. In the first case with consecutive jobs, it was assumed that the subject had changed jobs midway through the year, while in the second case it was assumed that the subject had worked complete years. In the first case the average of the two values for the cumulative MF exposure variable for the two jobs for the given year was taken while in the second case data management was straightforward.

In other cases, more than one job listed for a given year for a subject occurred because jobs were listed with overlap of the first and last years between different jobs. For example, a subject may have listed five jobs with the first and last years indicated as 1960 to 1965, 1962 to 1967, 1967 to 1970, 1970 to 1970, and 1971 to 1995. In this case, it could be assumed that for the overlap years (1962, 1963, 1964, 1965, and 1970) either the subject held two jobs during that year; or an error had been made. The overlap in years could, in general, not be explained by taking into account full- or part-time status of the listed jobs. Subjects with these types of overlapping job years were excluded from the primary analyses. However, in order to carry out the planned secondary sensitivity analyses, two additional year-by-year MF exposure files were created that included these subjects. In the first, the value for the MF cumulative exposure variable (i.e., the MF intensity exposure variable multiplied by the job status) for each year was calculated based upon the assumption that the subject held more than one job for the given year and may have worked more than 40 hours per week. Thus the values for the MF cumulative exposure variables for each job for the given year

were added together. This total may have been greater than 2. In the second file, it was assumed that the overlaps in job years were the result of an error, but the average value of the MF cumulative exposure values for each job was taken as the best estimate for that year rather than excluding the subject.

4.4.4 Analytic Study Populations

4.4.4.1 Analytic Study Populations for Sensitivity Analyses

As described earlier, there were many subjects with missing values for the start year and end year of jobs and/or instances where job years overlapped while the remainder of the data for these subjects were relatively complete in the NECSS data files. The primary analytic population was created by excluding all subjects with missing data for the start or end year for any job or with any overlapping years for different jobs suggestive of potential error. It was not actually necessary to have job year data for jobs where the exposure was not categorized above background in order to calculate the cumulative MF exposure index because the job duration was multiplied by zero in this index for all jobs with exposure at the background level. However, while most MF exposure indices could thus still be calculated for these subjects, the number of years worked could not. We considered that the number of years worked might be an important confounding factor in our risk analysis (due to the well-known healthy worker effect) and for this reason, did not take the exposure category into account when excluding subjects with missing or overlapping job years. In addition, we considered it possible that the data available for subjects with these types of missing data or data inconsistencies may be less reliable in general.

However, as a significant number of subjects were excluded from the primary analytic population, alternate methods of handling these particular data difficulties with job start and end years were explored in order to assess potential bias introduced by exclusion of subjects with missing or inconsistent job start and end year data. In total, one primary and four alternative analytic populations for sensitivity analyses were created. The composition of these populations is outlined in Table 4.4.

4.4.4.2 Analytic Study Populations for Analyses Based upon the Matched Pairs

In order to compare the results based upon the final unconditional logistic regression model with results from a conditional model where the pairing process used in the selection of controls was taken into account, a fifth secondary analytic study population was created. In this population, the matched pair for any subject excluded from the analysis in the baseline unconditional logistic regression model was excluded. We also excluded the pair containing the subject with incorrect age in original file and any pair with one subject missing data for covariates included in the final model.

4.5 Statistical Analyses

Overview

The statistical analyses included univariate descriptive analyses and multivariable analyses using logistic regression models. The descriptive analyses were carried out for the study population as defined in section 4.1. The multivariable analyses were carried out for the population that included only those subjects with complete and consistent occupational data; this population is referred to as the primary analytic population. The primary analyses involved unconditional logistic regression models although conditional logistic regression models were run for comparison. Secondary analyses were also

Table 4.4 Composition of the secondary analytic populations

	Primary analytic population	Secondary analytic population #1	Secondary analytic population #2	Secondary analytic population #3	Secondary analytic population #4
Subjects with complete job year dates for jobs held from age 18 or older	Included	Included	Included	Included	Included
Subjects with missing job years for jobs held from age 18 or older	Excluded	Excluded	Included unless exposure in job with missing dates was above background	Excluded	Included unless missing values could not be imputed
Subjects with missing job years for jobs held before age 18 or older	Included	Excluded	Included	Included	Included
Subjects with overlapping job years for jobs held from age 18 or older	Excluded	Excluded	Included unless exposure in one or more jobs with overlapping years was above background	Included	Included
Subjects with overlapping job year for jobs held before age 18	Included	Excluded	Included	Included	Included

carried out to explore: 1) alternate exposure indices; 2) alternate analytic populations which included subjects with missing or inconsistent occupational data; 3) subgroups based on NHL histology or topography; and 4) stratification by gender.

4.5.1 Descriptive Analyses

The distributions of selected characteristics and risk factors for NHL were presented as proportions for the cases and controls in the primary study population. Distributions by subtypes of NHL and by nodal status were presented as proportions of the case group. Job characteristics were also described.

4.5.2 Logistic Regression Model

Logistic regression models were constructed to estimate the risk of NHL associated with occupational exposure to MF above background levels. Given that NHL is a rare disease, the disease odds ratio provided by the logistic regression model could be used to estimate the relative risk of disease. The odds ratios associated with the parameters for the MF variable thus were used to estimate the relative risk of NHL due to occupational exposure to MF.

In constructing logistic regression models it was necessary to take into consideration that: a) frequency matching by sex and five-year age group had been carried out in the creation of the NECSS control sample; and b) our study control sample was chosen from the NECSS case-control population using pair matching by sex and five-year age group. Although some analysts suggest that logistic regression conditioned on the pairs is required when pair matching has been used in control selection, others, (including both Rothman[142] (pp. 147, 282) and Kleinbaum[143] (p. 379))

recommend that, when there is a large number of pairs that are not unique in terms of the matching factors, these pairs be pooled. When this pooling was undertaken, the number of variables required to define all sex-age group strata and all other risk factors was sufficiently small relative to the number of subjects that the use of unconditional logistic regression was considered unlikely to produce a biased result. Therefore, we chose to use an unconditional logistic regression model stratified by the matching factors (sex, five-year age group, and sex by five-year age group) as our primary model. However, we also conducted analyses using conditional regression stratified by the pairs and by the sex-age group strata. In addition, because the processes used for control selection in the NECSS differed between provinces, we considered it necessary to include province in all models.

The exposure index categories were treated as nominal variables in the model building phase. In the final analyses, the exposure index categories were entered as either a nominal variable in order to test for heterogeneity of the odds of NHL with each level of exposure or as a numerical variable in order to test for a linear trend in the odds of NHL with increasing level of exposure. The numerical value for each category was assigned the median value of the exposure index in that category. Specifically, the categories of background, low, medium, and high for cumulative MF exposure were assigned values of 0, 3, 11, and 32, respectively.

4.5.2.1 Unconditional Logistic Regression Model

As a first step in the model building process, unconditional logistic regression analyses of individual risk factors and risk of NHL controlled for the matching variables (sex, five-year age group, and sex by five-year age group terms) and province were carried out in order to identify variables to potentially include in a final model. The

potential risk factors evaluated in these preliminary analyses included: ever employed; number of years worked from age 18; income adequacy; education level; smoked 100+ cigarettes; number of pack-years smoked; self-reported work with benzene; self-reported work with pesticides and/or herbicides; self-reported work with radiation sources; expert-assessed occupational radiation exposure; use of electrical heating as the primary method of home heating; and self-reported work with welding at home. Self-reported work with welding at home and use of electrical heating as a primary method of home heating were considered as potential risk factors because we considered it possible that these factors may reflect exposure to MF in the non-work setting. Inclusion of these factors in the model may thus allow for partial control of unmeasured confounding due to non-work exposures in the risk assessment of NHL due to occupational exposure to MF. However, it should be noted that welding can include both arc welding and acetylene torch welding yet only arc welding results in exposure to MF. A p-value of 0.3 was considered suggestive for including a variable in the model.

The second step involved a search for confounders "based on the empirical principle of finding those covariates which, when included as stratification variables, changed the estimate of the disease-exposure odds ratio" as described by Siemiatycki *et al*.[144] Each potential confounding variable was included in a logistic regression model for NHL risk in addition to the nominal cumulative MF exposure variable, the matching variables, and the province identification variable in the baseline model. The results for the NHL disease odds ratio for MF from this model was compared to that from the baseline model without the potential confounder. If the odds ratio changed by more than 5% then it was considered that this variable was a confounder of the association between NHL risk and MF exposure and it was to be included in the final model. In

addition, if the width of the 95% confidence intervals of the NHL disease odds ratio for MF decreased by more than 10% from those in the baseline model, it was also considered important to include the potential confounding variable in the final model. These variables were to be included in order to improve precision despite the fact that they had not introduced any confounding. Potential confounding variables were evaluated in this manner on an individual basis.

The third step in the model building process involved the assessment of the remainder of the risk factors not included in the model after completion of the first two steps, with the exception of self-reported work with radiation sources at work, for the possibility of joint confounding of the NHL-MF association in the primary baseline model. Self-reported work with radiation sources was not assessed because expert-assessed radiation exposure was to be included in the baseline model.

Finally, the possibility of including interaction terms between MF exposure and other NHL risk factors in the primary model was to be considered only if a significant association between NHL risk and cumulative MF exposure was observed.

4.5.2.2 Conditional Logistic Regression Model

There is some controversy as to whether the pairing should be taken into account in the analysis when samples are formed using a pairing process. Conditional logistic regression would be the appropriate method to analyze a pair matched design. However, Rothman[142] and Kleinbaum[143] suggest that it is preferred to ignore the pairing when pairs are arbitrary. We examined the impact of this by running parallel conditional and unconditional logistic regressions. Conditional logistic regression stratified by the pairs was carried out using the variables selected in the final unconditional model where pooling had been implemented. In addition, because the possibility of bias exists with

the use of unconditional logistic regression if the number of subjects in all strata is not sufficiently large, conditional logistic regression based upon the sex-age group strata using the variables contained in the final model was also performed. The results for these analyses were compared with those from the unconditional logistic regression model based upon the same population (i.e., the population where the matched pair for each subject excluded was also excluded).

4.5.3 Exploratory and Sensitivity Analyses

All exploratory and sensitivity analyses were carried out using the final unconditional baseline model described above. The exploratory analyses included subgroup analyses, stratified analyses, and analyses using different indices of the exposure. These analyses were performed using the full primary analytic population (i.e., the population where subjects had complete and consistent occupational data and where the matched pair of an excluded subject was retained). The sensitivity analyses included analyses using the final model with different analytic populations and with differing assumptions regarding the interpretation of occupational data when their timing was not clear.

Secondary analyses were carried out in subgroups of NHL. These subgroups were based upon either histology or topography.

Stratified analyses were carried out by gender. Although we did not consider it likely that the biological effect of occupational MF exposure on NHL risk would vary by gender, we considered it possible that the results for males and females may differ. Firstly, we expected there to be more variability in the exposure in males than females leading to more informative results in the male strata compared to the female strata.

Secondly, distributions of MF exposures have been most often studied in men. Thus, there are less data available to assess MF exposure in jobs commonly held by females potentially yielding higher misclassification rates in women. It is also a possibility that exposures experienced by women may be different than those experienced by men in similar occupations.[145] Finally, several earlier studies of cancer risk and MF exposure have been carried out with males only.

Secondary analyses were carried out to explore the effect of using different exposure indices. These indices included cumulative MF exposure in different exposure time windows, cumulative MF exposure based upon different disease induction and latency period assumptions, and other indices to assess different aspects of dose. The exposure time windows studied included the time periods from 2-12, 13-22, 23-32, and 33-42 years before the interview date. A lag period of zero and of five years in addition to the primary two years was considered to account for differing induction and latency periods. The indices used to assess different aspects of dose included highest average exposure, average exposure in job held the longest, and duration of exposure above background levels.

Sensitivity analyses were carried out in an attempt to determine whether bias had been introduced by excluding subjects with missing or inconsistent job year data from the primary analyses. These analyses used the primary baseline model with populations that included additional or excluded further subjects in the primary analytic population and made differing assumptions in the interpretation of occupational data in calculating cumulative exposure. These populations and assumptions made are described in the data management section but, in summary, included the following modifications to the primary analytic population and cumulative MF exposure index:

- subjects with missing or overlapping job years for any job held before age 18 were also excluded (secondary analytic population #1);
- subjects with missing job or overlapping job years for jobs that did not involve exposure to MF above background were not excluded (secondary analytic population #2);
- subjects with overlapping job years were not excluded and exposure during the overlapping periods was either cumulated or averaged (secondary analytic population #3); and
- subjects with imputed values for missing job years and subjects with overlapping job years were not excluded and exposure was averaged for the overlapping time periods (secondary analytic population #4).

4.5.4 Computer Software Used

SAS Version 8.2 software was used for all analyses. Descriptive statistics were performed using the 'PROC FREQ' procedure. Unconditional regression was carried out using the 'PROC LOGISTIC' procedure. Tests for linear trend utilized the 'PROC LOGISTIC' procedure with each of the exposure categories coded with the median value of the continuous variable for that category and entered as a continuous variable. Conditional regression based upon the pairing was carried out using both the 'PROC LOGISTIC' procedure as described by Hosmer and Lemeshow[146] (pp. 190-3) and using the 'PROC PHREG' procedure as described by Kleinbaum.[147] Results were the same for the two procedures. The conditional regression based upon the sex-age group strata was performed using the 'PROC PHREG' procedure with creation of a new variable to identify each of the sex-age group strata.

CHAPTER 5
RESULTS

Overview

The results of our analyses of the risk of non-Hodgkin's lymphoma (NHL) associated with occupational exposure to power frequency magnetic fields (MF) in the case-control component of the National Enhanced Cancer Surveillance System (NECSS) are presented in this chapter. First, the results of the descriptive analyses of the demographic and potential NHL risk factors in our study population and the jobs held by the study subjects are presented. This is followed by the analytic results for the NHL-MF association. The acronym MF refers specifically to power frequency magnetic field exposure.

5.1 Descriptive Results

The final study population included 3,267 subjects: 1,624 cases of NHL and 1,643 controls. The results of the descriptive analysis of the demographic variables and possible predictor variables are presented in Table 5.1. There were slightly more males than females in our case population. Although the occurrence of NHL is more common in males than females, the cases included in the NECSS were sampled to make the number of males and females roughly equal. Age ranged from 20 to 76 years, with 75% of subjects above age 50. The distribution of cases and controls among the five-year age group strata was not exactly the same. Although the controls were selected by pair matching with cases by sex and five-year age group, this unequal distribution occurred because subjects were excluded from the study population after the selection of the controls and the matched pair of the excluded subject was retained in the study

Table 5.1 Distribution of selected characteristics and risk factors for 1,624 non-Hodgkin's lymphoma cases and 1,643 sex and age matched controls, NECSS, Canada 1994-1997

Factor	Cases		Controls	
	Number	%	Number	%
Sex				
Male	848	52.2	864	52.6
Female	776	47.8	779	47.4
Age (years)				
20-24	10	0.6	9	0.6
25-29	27	1.7	27	1.6
30-34	42	2.6	43	2.6
35-39	103	6.3	109	6.6
40-44	90	5.5	92	5.6
45-49	169	10.4	169	10.3
50-54	166	10.2	170	10.4
55-59	199	12.3	200	12.2
60-64	253	15.6	252	15.3
65-69	288	17.7	291	17.7
70-74	258	16.9	261	15.9
75+	19	1.2	20	1.2
Province				
Newfoundland	63	3.9	78	4.8
PEI	28	1.7	75	4.6
Nova Scotia	89	5.5	175	10.7
Ontario	616	37.9	637	38.8
Manitoba	106	6.5	101	6.2
Saskatchewan	102	6.3	80	4.9
Alberta	259	16.0	209	12.7
British Columbia	361	22.2	288	17.5
Subtype of NHL (Working Formulation)				
Low-grade	499	30.7		
Intermediate-grade	575	35.4		
High-grade	80	4.9		
Miscellaneous	89	5.5		
Unclassifiable	381	23.5		
Subtype of NHL (REAL System)				
Follicular	394	24.3		
Large B-cell	418	25.7		
Small lymphocytic	171	10.5		
Other or not classifiable	641	39.5		
Site of NHL				
Nodal	631	38.8		
Extranodal	285	17.5		
Not classifiable	708	43.7		
Ever employed				
Yes	1550	95.4	1548	94.2
No	74	4.6	95	5.6

Table 5.1 (con't.) Distribution of selected characteristics and risk factors for 1,624 non-Hodgkin's lymphoma cases and 1,643 age and sex matched controls, NECSS, Canada 1994-1997

Factor	Cases		Controls	
	Number	%	Number	%
Occupational MF exposure above background levels				
Ever	281	17.3	275	16.7
Never	1343	82.7	1368	83.3
Education				
Less than grade 12	803	49.5	786	47.8
Grade 12 or higher	816	50.3	851	51.8
Missing	5	0.3	6	0.4
Income adequacy				
Low	282	17.4	262	16.0
Lower-middle	228	14.0	284	17.3
Upper-middle	383	23.6	388	23.6
High	334	20.6	284	17.3
Missing	397	24.5	425	25.9
Smoked 100+ cigarettes				
Yes	1010	62.2	1033	62.9
No	613	37.8	606	36.9
Missing	1	0.1	4	0.2
Cigarette pack-years				
None	613	37.8	606	36.9
1 to 9	304	18.7	332	20.2
10 to 23	321	19.8	325	19.8
Greater than 23	355	21.9	344	20.9
Missing	31	1.9	36	2.2
Self-reported work with benzene				
Yes	54	3.3	51	3.1
No	1570	96.7	1592	1592
Self-reported work with pesticides				
Yes	248	15.3	196	11.9
No	1376	84.7	1447	88.1
Self-reported work with herbicides				
Yes	195	12.0	171	10.4
No	1429	88.0	1472	89.6
Self-reported work with pesticides or herbicides				
Yes	277	17.1	213	13.0
No	1347	82.9	1430	87.0
Expert-assessed ionizing radiation annual occupational exposure greater than 1 mSv				
Ever	46	2.8	29	1.8
Never	1578	97.2	1614	98.2

Table 5.1 (con't.) Distribution of selected characteristics and risk factors for 1,624 non-Hodgkin's lymphomas cases and 1,643 age and sex matched controls, NECSS, Canada 1994-1997

Factor	Cases		Controls	
	Number	%	Number	%
Self-reported work with radiation sources at work				
Yes	77	4.7	83	5.0
No	1547	95.3	1560	95.0
Use of electric heat as primary method of home heating				
Ever	646	39.8	593	36.1
Never	978	60.2	1049	63.9
Missing	0	0	1	0.1
Self-reported work with welding at home				
Yes	42	2.6	42	2.6
No	1582	97.4	1601	97.4

population. The largest number of subjects was from Ontario, followed by British Columbia and Alberta. The proportion of cases classified by the Working Formulation[17] as high-grade was 5%, which is smaller than expected. (In the analysis of Surveillance, Epidemiology, and End Results (SEER) data from 1978 to 1995, the proportion of the 60,057 cases of NHL cases that were classified as high-grade was 10%.)[12] This may have been a reflection of case recruitment procedures. Individuals diagnosed with NHL who had died within one to four months of diagnosis or those for whom consent was not granted by their physician were not included in the NECSS. These may have been the patients more likely to have the high-grade tumors. In addition, for nearly a quarter of the NHL cases the ICD-O histology code was too nonspecific to allow further classification of the cancer. In the 50% of cases in which nodal status could be determined, the proportion of extranodal lymphomas was 31%. This was somewhat higher than expected, but again may be a reflection of case recruitment procedures. (In the analysis the SEER data, 27% were extranodal.)[12]

Approximately 17% of subjects (17.3% of cases and 16.7% of controls) held a job for at least one year where the exposure to MF was assessed to be above background levels. Approximately 15% of subjects reported having worked with herbicides or pesticides, while only a small percentage (less than 5%) reported having worked with benzene or occupational radiation sources. The number assessed as having occupational exposure to radiation was similarly small; the number of study subjects who reported having worked with radiation sources in the occupational setting was greater than the number of subjects who had held one or more jobs where the expert-assessed annual ionizing radiation exposure greater than 1 mSv. Nearly 40% of subjects reported the use of electric heat as the primary method of home heating in

their primary residence at some time. Over 60% had a history of cigarette smoking. Information on income was missing for one quarter of subjects while information on education level was missing for less than 0.5% of subjects.

Of the 3,267 subjects in the study population, 169 (~5%) indicated that they had not worked outside the home. The remaining 3,098 subjects had held a total of 11,170 jobs. The descriptive analysis of the characteristics of these jobs by case/control status and by sex is presented in Table 5.2. The median number of jobs per subject was 3, and the median duration of these jobs was 4 years. Nearly 92% of the jobs were assessed as having only background levels of MF exposure (<0.3 μT), while over 99% were assessed as having less than 1 mSv annual exposure to ionizing radiation. The majority of the jobs assessed as having MF exposure above background levels were held by men.

In the study population, 106 subjects had jobs with missing job start or end years for at least one job held from age 18 or older; and 346 subjects had at least two jobs held from age 18 or older where the job years overlapped by more than one year. These subjects were excluded from the primary analytic population. The primary analytic population was thus made up of 2,815 subjects who had consistent information for occupational histories from age 18. The population based on the matched pairs of subjects (where a pair was excluded if data were missing on either member of the pair) consisted of 2,382 subjects (1,191 pairs).

Analytic populations were also created in order to carry out sensitivity analyses as described in the 'Data Management' section in Chapter 4. A total of 117 subjects had jobs with missing job start or end years for at least one job held at any age; and 355

Table 5.2 Distribution of selected characteristics for the 5,737 jobs of 1,550 employed non-Hodgkin's lymphoma cases and the 5,433 jobs of 1,548 employed controls, NECSS, Canada 1994-1997

Factor	Jobs of cases		Jobs of controls	
	Number	%	Number	%
Magnetic field exposure assessment				
Less than 0.3 μT	5,270	91.9	4,944	91.0
0.3 to less than 0.6 μT	320	5.6	346	6.7
0.6 μT or greater	147	2.6	143	2.6
Jobs held by males				
Less than 0.3 μT	2,987	88.4	2,797	87.2
0.3 to less than 0.6 μT	266	7.9	290	9.1
0.6 μT or greater	128	3.8	119	3.7
Jobs held by females				
Less than 0.3 μT	2,283	96.9	2,147	96.4
0.3 to less than 0.6 μT	54	2.3	56	2.5
0.6 μT or greater	19	0.8	24	1.1
Annual exposure to ionizing radiation assessment				
1 mSv or less	5,674	98.9	5,395	99.3
Greater than 1 mSv	63	1.1	38	0.7
	Mean/ median	**Range**	**Mean/ Median**	**Range**
Number of jobs per subject*	3.6/3	1-12	3.4/3	1-11
Duration of jobs (years)**	7.6/4	1-55	7.8/4	1-54

* Based on subjects that held at least one job from age 18 years.
** Excludes 202 jobs where duration was unknown and 326 jobs which were held by subjects before age 18.

subjects had at least two jobs held at any age where the job years overlapped by more than one year. The population where these subjects were excluded (secondary population #1) consisted of 2,795 subjects. The population that excluded only subjects with missing or inconsistent job year data for jobs with MF exposures above background (secondary population #2) consisted of 3,217 subjects. The population that excluded only subjects with missing data for job start or end year for at least one job held from age 18 or older while including those with jobs where the job years overlapped by more than one year (secondary population #3) consisted of 3,161 subjects. Finally, the population that excluded only subjects with missing data for job start or end years after imputation of these missing elements was carried out (secondary population #4) consisted of 3,256 subjects.

The distribution of the cumulative MF exposure index with a two-year lag for the 221 cases and 233 controls in the primary analytic population with exposure above background levels is shown in the histogram in Figure 5.1. It ranged from greater than 0 to 92. A total of 2,361 subjects (84%) had cumulative exposures of 0, (i.e., only background exposures). The tertiles of this index in those subjects with exposures above background were 6.0 and 20.0; the median values for each of these three groups were 3, 11, and 32.

5.2 Analytic Results

5.2.1 Preliminary Analyses of Potential Risk Factors

In the preliminary unconditional logistic model, adjusted for sex, five-year age group, sex by five-year age group, and province, the risk of NHL did not vary significantly with cumulative MF occupational exposure (Table 5.3). There was no

Figure 5.1 Histogram of the distribution of the cumulative magnetic field exposure index in the 221 cases and 233 controls with exposures above background in the primary analytic population, NECSS, Canada 1994-1997

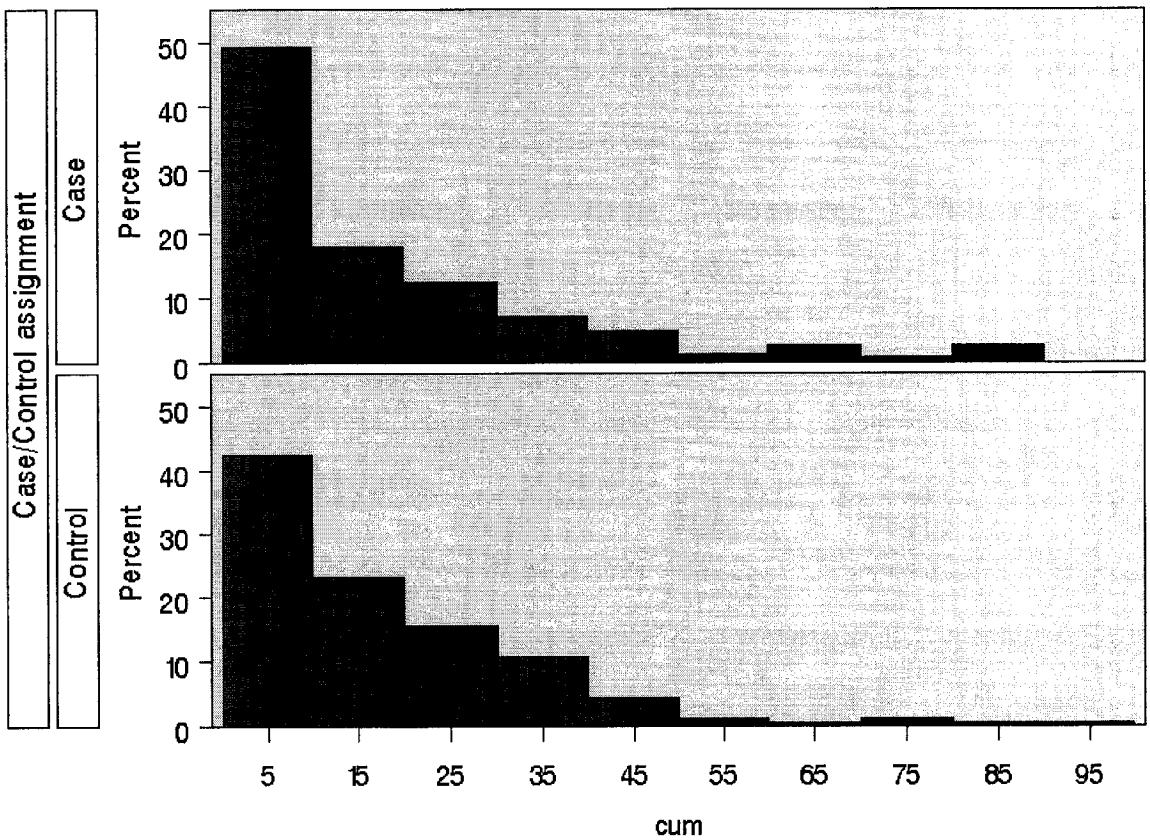


Table 5.3 Preliminary analysis of potential risk factors in 1,377 non-Hodgkin's lymphoma cases and 1,438 controls, NECSS, Canada 1994-1997*

Risk Factor	Distribution among cases and controls		Odds ratio (95% CI)	P-value for hetero-geneity / p-value for trend*
	Cases	Controls		
Cumulative EMF exposure				
None	1,156	1,205	1	0.38 / 0.66
Low	78	64	1.25 (0.88-1.77)	
Medium	71	89	0.83 (0.60-1.16)	
High	72	80	0.98 (0.69-1.37)	
Ever employed				
No	74	95	1	0.13
Yes	1,303	1,343	1.29 (0.93-1.80)	
Number of years worked from age 18				
None	75	96	1	0.46 / 0.20
0.5 to <19 (median 11)	421	443	1.24 (0.88-1.75)	
19 to < 33.5 (median 26)	439	456	1.31(0.92-1.86)	
33.5 to 58 (median 40)	442	443	1.34 (0.92-1.96)	
Education				
Less than grade 12	683	689	1	0.10
Grade 12 or higher	690	744	0.87 (0.74-1.03)	
Missing	4	5	-	
Income adequacy				
High	282	250	1	0.05 / 0.62
Upper-middle	325	343	0.86 (0.68-1.08)	
Lower-middle	195	247	0.72 (0.55-0.94)	
Low	236	230	0.99 (0.76-1.29)	
Missing	339	368	-	
Income adequacy with missing included as a category				
High	282	250	1	0.08
Upper-middle	325	343	0.85 (0.68-1.08)	
Lower-middle	195	247	0.71 (0.54-0.92)	
Low	236	230	0.96 (0.74-1.24)	
Missing	339	368	0.84 (0.67-1.07)	
Income adequacy missing				
No	1,038	1,070	1	0.69
Yes	339	368	0.97 (0.81-1.15)	

*Analyses adjusted for sex, five-year age group, sex by five-year age group, and province. Subjects with missing values for a given risk factor were excluded from analyses.
** Test of trend for categorical variables with more than two levels was based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous variable for the category in place of the categorical variable.

Table 5.3 (con't.) Preliminary analysis of potential risk factors in 1,377 non-Hodgkin's lymphoma cases and 1,438 controls, NECSS, Canada 1994-1997*

Risk Factor	Distribution among cases and controls		Odds ratio (95% CI)	P-value for hetero-geneity / p-value for trend**
	Cases	Controls		
Smoked 100+ cigarettes				
No	523	541	1	0.95
Yes	853	893	1.01 (0.86-1.18)	
Missing	1	4	-	
Cigarette pack-years				
None	523	541	1	0.69 / 0.35
1 to 9 (median 4)	254	280	0.93 (0.75-1.15)	
10 to 23 (median 16)	272	284	1.01 (0.82-1.25)	
>23 (median 35)	305	302	1.08 (0.87-1.34)	
Missing	23	31	-	
Self-reported work with benzene				
No	1,332	1,390	1	0.97
Yes	45	48	1.01 (0.66-1.54)	
Self-reported work with pesticides				
No	1,185	1,277	1	0.08
Yes	192	161	1.23 (0.97-1.55)	
Self-reported work with herbicides				
No	1,224	1,301	1	0.35
Yes	153	137	1.13 (0.88-1.46)	
Self-reported work with pesticides or herbicides				
No	1,164	1,265	1	0.03
Yes	213	173	1.28 (1.02-1.60)	
Expert-assessed ionizing radiation annual occupational exposure greater than 1 mSv				
Never	1,341	1,412	1	0.17
Ever	36	26	1.45 (0.86-2.43)	
Self-reported work with radiation sources at work				
No	1,316	1,371	1	0.71
Yes	61	67	0.93 (0.65-1.34)	

*Analyses adjusted for sex, five-year age group, sex by five-year age group, and province. Subjects with missing values for a given risk factor were excluded from analyses.
** Test of trend for categorical variables with more than two levels was based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous variable for the category in place of the categorical variable.

Table 5.3 (con't.) Preliminary analysis of potential risk factors in 1,377 non-Hodgkin's lymphoma cases and 1,438 controls, NECSS, Canada 1994-1997*

Risk Factor	Distribution among cases and controls		Odds ratio (95% CI)	P-value for hetero-geneity / p-value for trend**
	Cases	Controls		
Use of electric heat as primary method of home heating				
Never	538	508	1	0.04
Ever	839	929	1.18 (1.01-1.39)	
Missing	0	1	-	
Self-reported work with welding at home				
No	1,343	1,410	1	0.44
Yes	34	28	1.23 (0.73-2.05)	

*Analyses adjusted for sex, five-year age group, sex by five-year age group, and province. Subjects with missing values for a given risk factor were excluded from analyses.
** Test of trend for categorical variables with more than two levels was based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous variable for the category in place of the categorical variable.

evidence of a trend of increasing risk with increasing exposure.

The results of the unconditional logistic regressions for each of the individual potential risk factors for NHL are also presented in Table 5.3. Each of these analyses was controlled for the matching factors and for province; each was carried out using all subjects in the primary analytic population except those with missing values for the particular risk factor. Several factors were found to be associated with NHL risk (p-values less than 0.3), although the odds ratios were not high. Both a history of any employment and the number of years worked were negatively associated with the risk of NHL. Contrary to our expectations based on the healthy worker effect, in our study population it appeared that workers had a greater risk of NHL than did non-workers, and that the risk was higher in workers with increased duration of work. In addition, work with pesticides or herbicides, occupational exposure to radiation, and ever use of electric home heat as the primary method of heating were associated with a higher NHL risk while higher education level was associated with a lower NHL risk. Although the p-value for the association between income and NHL was also less than 0.3, there was no trend in the apparent associations between the ordered categories and there was a large proportion of subjects with missing data for this variable (25%). Of note, neither of smoking nor work with benzene was found to be a risk factor for NHL in these preliminary analyses.

5.2.2 Assessment of Confounding

The results of the assessment for confounding of the NHL-MF association by potential risk factors on an individual basis are presented in Table 5.4. The NHL odds ratios for cumulative MF exposure adjusted for only the matching factors and province

Table 5.4 Assessment of potential confounding by individual risk factors of the association between non-Hodgkin's lymphoma risk and occupational cumulative magnetic field exposure among 1,377 cases and 1,438 controls, NECSS, Canada 1994-1997*

Potential confounding variable	Cumulative MF exposure	Model of risk of NHL associated with occupational cumulative MF exposure		Number of subjects**
		Without potential confounding variable	With potential confounding variable	
		Odds ratio (95% CI)	Odds ratio (95% CI)	
Ever employed	Background	1	1	2,815
	Low	1.25 (0.88-1.77)	1.24 (0.87-1.75)	
	Medium	0.83 (0.60-1.16)	0.82 (0.59-1.14)	
	High	0.98 (0.69-1.37)	0.97 (0.69-1.36)	
Number of years worked from age 18	Background	1	1	2,815
	Low	1.25 (0.88-1.77)	1.23 (0.87-1.75)	
	Medium	0.83 (0.60-1.16)	0.82 (0.59-1.15)	
	High	0.98 (0.69-1.37)	0.96 (0.68-1.36)	
Education	Background	1	1	2,806
	Low	1.25 (0.88-1.77)	1.23 (0.87-1.74)	
	Medium	0.83 (0.60-1.15)	0.81 (0.58-1.13)	
	High	0.98 (0.69-1.38)	0.96 (0.68-1.35)	
Income adequacy	Background	1	1	2,108
	Low	1.03 (0.69-1.56)	1.06 (0.70-1.60)	
	Medium	0.96 (0.65-1.40)	0.98 (0.67-1.44)	
	High	0.99 (0.67-1.47)	1.04 (0.70-1.54)	
Smoked 100+ cigarettes	Background	1	1	2,810
	Low	1.25 (0.88-1.76)	1.25 (0.88-1.76)	
	Medium	0.83 (0.60-1.15)	0.83 (0.59-1.15)	
	High	0.97 (0.69-1.37)	0.97 (0.69-1.37)	
Cigarette pack-years	Background	1	1	2,761
	Low	1.17 (0.82-1.66)	1.17 (0.82-1.66)	
	Medium	0.84 (0.60-1.17)	0.83 (0.59-1.16)	
	High	0.96 (0.68-1.35)	0.95 (0.68-1.35)	
Self-reported work with benzene	Background	1	1	2,815
	Low	1.25 (0.89-1.77)	1.25 (0.88-1.77)	
	Medium	0.83 (0.60-1.16)	0.83 (0.60-1.16)	
	High	0.98 (0.70-1.38)	0.98 (0.69-1.37)	
Self-reported work with pesticides	Background	1	1	2,815
	Low	1.25 (0.88-1.77)	1.23 (0.87-1.75)	
	Medium	0.83 (0.60-1.16)	0.83 (0.59-1.15)	
	High	0.98 (0.69-1.37)	0.97 (0.69-1.37)	
Self-reported work with herbicides	Background	1	1	2,815
	Low	1.25 (0.88-1.77)	1.25 (0.88-1.76)	
	Medium	0.83 (0.60-1.16)	0.83 (0.60-1.15)	
	High	0.98 (0.69-1.37)	0.98 (0.69-1.37)	

*All analyses were adjusted for sex, five-year age group, sex by five-year age group, and province.
**Subjects with missing values for the potential confounding variable were excluded from the analysis.

Table 5.4 (con't.) Assessment of potential confounding by individual risk factors of the association between non-Hodgkin's lymphoma risk and occupational cumulative magnetic field exposure among 1,377 cases and 1,438 controls, NECSS, Canada 1994-1997*

Potential confounding variable	Cumulative MF exposure level	Model of risk of NHL associated with occupational cumulative MF exposure: Without potential confounding variable — Odds ratio (95% CI)	With potential confounding variable — Odds ratio (95% CI)	Number of subjects**
Self-reported work with pesticides or herbicides	Background	1	1	2,815
	Low	1.25 (0.88-1.77)	1.23 (0.87-1.75)	
	Medium	0.83 (0.60-1.16)	0.83 (0.59-1.15)	
	High	0.98 (0.69-1.37)	0.97 (0.69-1.37)	
Expert-assessed ionizing radiation annual occupational exposure greater than 1 mSv	Background	1	1	2,815
	Low	1.25 (0.88-1.77)	1.23 (0.87-1.74)	
	Medium	0.83 (0.60-1.16)	0.83 (0.59-1.15)	
	High	0.98 (0.69-1.37)	0.97 (0.69-1.36)	
Self-reported work with radiation sources at work	Background	1	1	2,815
	Low	1.25 (0.88-1.77)	1.25 (0.88-1.77)	
	Medium	0.83 (0.60-1.16)	0.83 (0.60-1.16)	
	High	0.98 (0.69-1.37)	0.98 (0.70-1.39)	
Use of electric heat as primary method of home heating	Background	1	1	2,814
	Low	1.25 (0.88-1.77)	1.26 (0.89-1.78)	
	Medium	0.83 (0.60-1.15)	0.84 (0.60-1.17)	
	High	0.97 (0.69-1.37)	0.98 (0.69-1.38)	
Self-reported work with welding at home	Background	1	1	2,815
	Low	1.25 (0.88-1.77)	1.24 (0.88-1.76)	
	Medium	0.83 (0.60-1.16)	0.82 (0.59-1.15)	
	High	0.98 (0.69-1.37)	0.98 (0.69-1.37)	

*All analyses were adjusted for sex, five-year age group, sex by five-year age group, and province.
**Subjects with missing values for the potential confounding variable were excluded from the analysis.

are presented in the third column while the NHL odds ratios for MF exposure adjusted for the matching factors and province as well as for the potential confounding risk factor are presented in the fourth column. Each of the two analyses for each potential confounding risk factor was carried out using the primary analytic population excluding subjects with missing values for the variable being assessed. The size of this population for the two analyses for each variable is provided in the fifth column. Potential confounding risk factors were assessed individually. None of the odds ratios changed by more than 5%, nor did the width of the confidence intervals change by more than 5% in these analyses.

We decided to include, in addition to the matching variables and province, in the baseline model the variables: education, cigarette pack-years, number of years worked from age 18, work with pesticides or herbicides, occupational exposure to ionizing radiation, and use of electric heat as a method of home heating. Although none of these variables appeared to produce confounding of the NHL-MF association, they were included for other reasons. The number of years worked was included as the preliminary analyses of risk factors for NHL suggested an increased risk for workers compared to non-workers and increased risk for workers with longer duration of work. Although this was contrary to our expectations, it was considered necessary to either limit our study to workers or to adjust for this factor in the analysis. We opted for the second alternative. Education and cigarette pack-years were included to increase the credibility of our results as these factors often cause confounding in occupational studies. Self-reported work with pesticides or herbicides, expert-assessed radiation exposure, and cigarette pack-years were included as these have been considered potential risk factors for NHL in the literature and the results of their association with

NHL risk in our study were of some interest. In addition, education, self-reported work with pesticides or herbicides, and expert-assessed exposure to occupational radiation each were associated with p-values less than 0.3 in the preliminary analyses of NHL risk. The use of electric heat as a primary method of home heating was included in the model because of its significant association with NHL in the preliminary analysis of individual risk factors. It was believed that this variable was potentially a surrogate for some other factor and thus was of interest to explore further. Income adequacy was not included because values for this variable were missing for a large number of subjects, and it was believed that the inclusion of education in the model would account for most of the effects of social economic status. In addition, we believed that income may be too closely related to occupation and thus be a surrogate for exposure and result in over-adjustment. The matching variables and province were necessarily included for methodological reasons.

Following the determination of this baseline model, the remaining potential risk factors were assessed for joint confounding of the NHL-MF association. The results of this assessment are presented in Table 5.5. There was no evidence of joint confounding nor was there evidence of change in the precision of the NHL-MF association estimates.

5.2.3 Primary Model

Our primary logistic regression model thus included the variables: cumulative MF exposure, sex, five-year age group, sex by five-year age group, province, education, cigarette pack-years, number of years worked from age 18, work with pesticides or herbicides, occupational exposure to ionizing radiation, and use of electric heat as a method of home heating. This model was based upon 2,751 subjects as 64 subjects in

Table 5.5 Assessment of potential joint confounding of the association of non-Hodgkin's lymphoma risk and occupational cumulative magnetic field exposure among 1,377 cases and 1,438 controls, NECSS, Canada 1994-1997*

Potential confounding variable(s)	Cumulative MF exposure	Model of risk of NHL associated with occupational cumulative MF exposure		Number of subjects**
		Without potential confounding variable	With potential confounding variable	
		Odds ratio (95% CI)	Odds ratio (95% CI)	
Income adequacy	Background	1	1	2,061
	Low	0.95 (0.62-1.45)	0.97 (0.64-1.48)	
	Medium	0.94 (0.64-1.39)	0.96 (0.65-1.42)	
	High	0.98 (0.66-1.46)	1.03 (0.69-1.53)	
Self-reported work with welding at home	Background	1	1	2,751
	Low	1.10 (0.77-1.58)	1.10 (0.77-1.57)	
	Medium	0.80 (0.57-1.13)	0.80 (0.57-1.12)	
	High	0.92 (0.65-1.30)	0.92 (0.65-1.30)	
Self-reported work with benzene	Background	1	1	2,751
	Low	1.10 (0.77-1.58)	1.10 (0.77-1.58)	
	Medium	0.80 (0.57-1.13)	0.81 (0.58-1.13)	
	High	0.92 (0.65-1.30)	0.92 (0.65-1.30)	
Income adequacy, self-reported work with welding at home, self-reported work with benzene	Background	1	1	2,061
	Low	0.95 (0.62-1.45)	0.96 (0.63-1.46)	
	Medium	0.94 (0.64-1.39)	0.95 (0.64-1.41)	
	High	0.98 (0.66-1.46)	1.03 (0.69-1.53)	

*Baseline model included sex, five-year age group, sex by five-year age group, province, cumulative MF exposure, number of year worked from age 18, education, cigarette pack-years, work with pesticides or herbicides, use of electric home heat, and occupational radiation exposure.
**Subjects with missing values for the potential confounding variable(s) were excluded from the analysis.

the primary analytic population had missing values for one or more of the covariates included in the final model. Because no significant association between cumulative MF exposure and NHL risk was observed, potential interactions between MF exposure and other NHL risk factors were not assessed.

The results from the primary model are presented in Table 5.6. There was no significant association of cumulative MF exposure and risk of NHL, and no evidence of a trend of increasing risk with increasing exposure. The associations noted in the preliminary analyses for the other risk factors did not change significantly in this multivariable model. Of note, the risk of NHL associated with work with pesticides or herbicides was increased by approximately 30% (OR 1.3, 95% CI: 1.0, 1.6) and the use of electric heat as a primary method of home heating was associated with a 20% increase in risk (OR 1.2, 95% CI: 1.0, 1.4); both of these associations were significant at the 5% level. Expert-assessed ionizing radiation annual occupational exposure greater than 1 mSv was also associated with a 30% increase in risk, but the p-value associated with this estimate was 0.29.

5.2.4 Conditional Models

The comparisons of the results of the primary model described above with conditional models are presented in Table 5.7. The results of the conditional logistic regression for cumulative MF exposure where the individual pairs were retained and province and the six covariates included in the primary model were controlled for are presented in the first row of data in Table 5.7. This analysis was based upon 1,137 pairs (54 pairs were excluded due to missing data for one or more covariates). The results for the conditional logistic regression stratified by sex-age group categories (i.e.,

Table 5.6 Primary model of the risk of non-Hodgkin's lymphoma for 1,350 cases and 1,401 controls, NECSS, Canada 1994-1997*

Risk factor	Odds ratio (95% CI)	P-value for heterogeneity / p-value for trend**
Cumulative MF exposure		
Background	1	0.53 / 0.42
Low	1.10 (0.77-1.58)	
Medium	0.80 (0.57-1.13)	
High	0.92 (0.65-1.30)	
Number of years worked from age 18		
None (median 0)	1	0.43 / 0.22
0.5 to <19 (median 11)	1.27 (0.89-1.81)	
19 to<33.5 (median 26)	1.35 (0.93-1.94)	
3.5 to 58 (median 40)	1.36 (0.92-2.00)	
Education		
Less than grade 12	1	0.09
Grade 12 or higher	0.87 (0.73-1.02)	
Cigarette pack years		
None (median 0)	1	0.71 / 0.50
1 to 9 (median 4)	0.91 (0.74-1.13)	
10 to 23 (median 16)	0.98 (0.79-1.22)	
> 23 (median 35	1.05 (0.85-1.31)	
Self-reported work with pesticides or herbicides		
No	1	0.03
Yes	1.28 (1.02-1.61)	
Use of electric heat as primary method of home heating		
Never	1	0.04
Ever	1.19 (1.01-1.40)	
Expert-assessed ionizing radiation annual exposure greater than 1 mSv		
Never	1	0.29
Ever	1.33 (0.79-2.26)	

* Analysis adjusted for sex, five-year age group, sex by five-year age group, and province. Sixty-four subjects excluded due to missing values for either education, cigarette pack-years, or use of electric heat as primary method of home heating.

** Test of trend for categorical variables with more than two categories was based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous variable for the category in place of the categorical variable.

Table 5.7 Conditional and unconditional regression models of the risk of non-Hodgkin's lymphoma associated with occupational cumulative magnetic field exposure among 1,137 cases and 1,137 controls, NECSS, Canada 1994-1997*

Cumulative MF exposure	Cases	Controls	Odds ratio (95% CI)	P-value for heterogeneity / p-value for trend**
Conditional regression with stratification by pairs model				
Background	956	950	1	0.30 / 0.71
Low	62	51	1.13 (0.76-1.67)	
Medium	56	74	0.71 (0.48-1.04)	
High	63	62	1.02 (0.68-1.52)	
Conditional regression with stratification by sex and five-year age group category (i.e., pooling) model				
Background	956	950	1	0.35 / 0.79
Low	62	51	1.14 (0.77-1.69)	
Medium	56	74	0.74 (0.51-1.07)	
High	63	62	1.03 (0.71-1.51)	
Unconditional regression adjusting for sex, five-year age group, and sex*five-year age group model				
Background	956	950	1	0.35 / 0.71
Low	62	51	1.12 (0.75-1.66)	
Medium	56	74	0.73 (0.50-1.06)	
High	63	62	1.02 (0.69-1.49)	

*All models were adjusted for province, number of years worked from age 18, education, cigarette pack-years, work with pesticides or herbicides, use of electric home heat, and radiation exposure.
** Test of trend for cumulative MF exposure based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous cumulative MF exposure index for the category in place of the categorical cumulative MF exposure variable.

pooling of the pairs) and controlled for province and the other six covariates for the same 2,382 subjects are presented in the second row of data. Finally, the results for the unconditional logistic regression controlling for five-year age group, sex, and five-year age group by sex, as well as for province and the other six covariates for the 2,382 subjects are presented in the third row of data. There was no evidence from these results that bias had been introduced by pooling the matched pairs with common values for the matching factors, nor from carrying out unconditional logistic regression. Therefore, all further results were carried out using unconditional logistic regression models with the matching variables included in the model.

5.2.5 Other Exposure Indices

Analyses of the alternate exposure indices using the primary model (unconditional logistic regression adjusted for sex, five-year age-group, sex by five-year age group, province, number of years worked from age 18, education, cigarette pack-years, work with pesticides or herbicides, use of electric home heat, and radiation exposure) and the 2,815 subjects in the primary analytic population are presented in Table 5.8. Of note, the results did not vary significantly with the use of these different indices. There was no apparent association between occupational MF exposure and NHL risk.

5.2.6 Sensitivity Analyses

The results of the analyses done using the various populations are presented in Table 5.9. The results appeared insensitive to the differing assumptions made in forming these populations or in resolving inconsistencies in job year data.

Table 5.8 Risk of non-Hodgkin's lymphoma associated with alternate occupational magnetic field exposure indices among 1,350 cases and 1,401 controls, NECSS, Canada 1994-1997*

Exposure index	Distribution among cases and controls		Odds ratios (95% CI)	P-value for heterogeneity / p-value for trend**
	Cases	Controls		
Cumulative MF exposure with a 2-year lag period				
Background	1,134	1,171	1	0.53 / 0.42
Low	74	64	1.10 (0.77-1.58)	
Medium	71	87	0.80 (0.57-1.13)	
High	71	79	0.92 (0.65-1.30)	
Cumulative MF exposure for jobs held at all ages with a 2-year lag period***				
Background	1,118	1,161	1	0.74 / 0.42
Low	73	68	1.03 (0.72-1.46)	
Medium	72	84	0.85 (0.60-1.19)	
High	73	82	0.90 (0.64-1.27)	
Cumulative MF exposure with no lag period				
Background	1,133	1,169	1	0.48 / 0.34
Low	74	63	1.12 (0.79-1.60)	
Medium	70	85	0.80 (0.57-1.13)	
High	73	84	0.89 (0.63-1.25)	
Cumulative MF exposure with a 5-year lag period				
Background	1,139	1,173	1	0.17 / 0.54
Low	77	66	1.13 (0.79-1.60)	
Medium	63	89	0.70 (0.49-0.98)	
High	71	73	0.99 (0.69-1.41)	
Cumulative MF exposure in the 3-12 year time window				
Background	1,251	1,289	1	0.91 / 0.50
Low	26	29	0.96 (0.55-1.66)	
Medium	30	32	0.97 (0.58-1.63)	
High	43	51	0.85 (0.56-1.31)	
Cumulative MF exposure in the 13-22 year time window				
Background	1,226	1,270	1	0.79 / 0.67
Low	43	39	1.19 (0.73-1.94)	
Medium	22	28	0.84 (0.49-1.43)	
High	59	64	0.95 (0.65-1.39)	

*All analyses were adjusted for sex, five-year age group, sex by five-year age group, province, number of years worked from age 18, education, cigarette pack-years, work with pesticides or herbicides, occupational radiation exposure, and use of electric home heat.

** Test of trend for categorical exposure indices with more than two levels was based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous exposure index for the category in place of the categorical exposure variable.

*** This analysis was based upon 1,336 cases and 1,395 controls due to the exclusion of subjects with missing values for job years or overlapping jobs for jobs held before age 18.

Table 5.8 (con't.) Risk of non-Hodgkin's lymphoma associated with alternate occupational magnetic field exposure indices among 1,350 cases and 1,401 controls, NECSS, Canada 1994-1997*

Exposure index	Distribution among cases and controls		Odds ratios (95% CI)	P-value for heterogeneity / p-value for trend**
	Cases	Controls		
Cumulative MF exposure in the 23-32 year time window				
None	1,235	1,273	1	0.93 / 0.67
Low	41	45	0.92 (0.59-1.44)	
Medium	26	30	0.85 (0.49-1.48)	
High	48	53	0.97 (0.64-1.47)	
Cumulative MF exposure in the 33-42 year time window				
None	1,259	1,302	1	0.76 / 0.93
Low	39	38	1.04 (0.65-1.67)	
Medium	16	29	0.57 (0.30-1.06)	
High	36	32	1.14 (0.69-1.89)	
Highest MF exposure intensity in any job				
Less than 0.3 μT	1,134	1,171	1	0.68 / 0.71
0.3 to less than 0.6 μT	144	162	0.90 (0.70-1.16)	
0.6 μT or greater	72	68	1.04 (0.73-1.48)	
MF exposure intensity in job held longest				
Less than 0.3 μT	1,253	1,281	1	0.24 / 0.36
0.3 to less than 0.6 μT	62	86	0.74 (0.52-1.05)	
0.6 μT or greater	35	34	1.00 (0.61-1.64)	
Number of years worked in jobs with MF exposure above background				
None	1,134	1,171	1	0.23 / 0.15
0.25 to < 5 (median 2.5)	74	58	1.24 (0.86-1.79)	
5 to < 17.5 (median 8.5)	76	88	0.82 (0.59-1.15)	
17.5 to 50 (median 26)	66	84	0.81 (0.57-1.15)	

*All analyses were adjusted for sex, five-year age group, sex by five-year age group, province, number of years worked from age 18, education, cigarette pack-years, work with pesticides or herbicides, occupational radiation exposure, and use of electric home heat.

** Test of trend for categorical exposure indices with more than two levels was based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous exposure index for the category in place of the categorical exposure variable.

*** This analysis was based upon 1,336 cases and 1,395 controls due to the exclusion of subjects with missing values for job years or overlapping jobs for jobs held before age 18.

Table 5.9 Risk of non-Hodgkin's lymphoma associated with occupational cumulative magnetic field exposure in different analytic populations, NECSS, Canada 1994-1997*

Population (sample size)	Cumulative MF exposure	Distribution among cases and controls		Odds ratio (95% CI)	P-value for hetero-geneity / p-value for trend**
		Cases	Controls		
Primary population (n=2,751)	Background	1,134	1,171	1	0.53 / 0.42
	Low	74	64	1.10 (0.77-1.58)	
	Medium	71	87	0.80 (0.57-1.13)	
	High	71	79	0.92 (0.65-1.30)	
Population with subjects with missing or overlapping years for jobs held at any age excluded (n=2,731)	Background	1,121	1,168	1	0.62 / 0.46
	Low	74	64	1.11 (0.78-1.58)	
	Medium	71	85	0.83 (0.59-1.16)	
	High	70	78	0.92 (0.65-1.31)	
Population with subjects with missing or overlapping years for jobs with exposure at background levels included*** (n=3,139)	Background	1,323	1,338	1	0.80 / 0.65
	Low	81	71	1.07 (0.76-1.50)	
	Medium	77	87	0.87 (0.62-1.20)	
	High	79	83	0.96 (0.69-1.34)	
Population with subjects with jobs with overlapping years included (exposure cumulated for overlapping years) (n=3,161)	Background	1,274	1,302	1	0.81 / 0.64
	Low	92	79	1.09 (0.79-1.50)	
	Medium	81	90	0.89 (0.64-1.22)	
	High	83	87	0.95 (0.69-1.32)	
Population with subjects with jobs with overlapping years included (exposure averaged for overlapping years) (n=3,161)	Background	1,274	1,302	1	0.80 / 0.62
	Low	94	81	1.09 (0.80-1.50)	
	Medium	82	90	0.89 (0.65-1.23)	
	High	80	85	0.95 (0.68-1.32)	
Population with subjects with jobs with imputed years included (exposure averaged for overlapping years) (n=3,177)	Background	1,320	1,333	1	0.86 / 0.61
	Low	94	81	1.08 (0.79-1.48)	
	Medium	86	92	0.91 (0.67-1.25)	
	High	83	88	0.94 (0.68-1.30)	

* All analyses were adjusted for sex, five-year age group, sex by five-year age group, province, number of years worked from age 18, education, cigarette pack-years, work with pesticides or herbicides, occupational radiation exposure, and use of electric home heat.

** Test of trend for cumulative MF exposure based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous cumulative MF exposure index for the category in place of the categorical cumulative MF exposure variable.

*** This analysis was controlled for ever/never worked rather than number of years worked from age 18 as the value for this variable was unknown for some subjects in this analytic population.

5.2.7 Subgroup Analyses

The results of the analyses carried out for subtypes of NHL are presented in Table 5.10. The risk appeared to decrease with exposure for both the follicular and diffuse large cell subtypes. This was considered most likely a result of multiple testing and not a reflection of a true association. Of more interest was the observation that the risk of extranodal lymphomas tended to increase with increasing levels of cumulative MF exposure, although again it was likely the result of multiple testing.

5.2.8 Stratified by Sex Analyses

The results did not differ by sex. The precision of the estimates was greater in the male strata than in the female; the precision of the estimates for the overall group was somewhat greater than that in the male strata. These results are presented in Table 5.11.

Table 5.10 Risk of non-Hodgkin's lymphoma associated with occupational cumulative magnetic field exposure in different subgroups, NECSS, Canada 1994-1997*

Population (sample size)	Cumulative MF exposure	Cases	Controls	Odds ratios (95% CI)	P-value for heterogeneity / p-value for trend**
Primary analytic population (1,350 cases, 1,401 controls)	Background	1,134	1,171	1	0.53 / 0.42
	Low	74	64	1.10 (0.77-1.58)	
	Medium	71	87	0.80 (0.57-1.13)	
	High	71	79	0.92 (0.65-1.30)	
Subgroups based on Working Formulation[17]					
Low-grade (416 cases, 1,401 controls)	Background	356	1,171	1	0.59 / 0.24
	Low	22	64	1.07 (0.64-1.80)	
	Medium	21	87	0.77 (0.46-1.28)	
	High	17	79	0.76 (0.44-1.34)	
Intermediate- and high-grade (548 cases, 1,401 controls)	Background	471	1,171	1	0.15 / 0.03
	Low	28	64	0.97 (0.60-1.55)	
	Medium	28	87	0.71 (0.45-1.12)	
	High	21	79	0.61 (0.37-1.03)	
Subgroups based on REAL classification[19]					
Follicular (336 cases, 1,401 controls)	Background	293	1,171	1	0.32 / 0.08
	Low	17	64	0.99 (0.56-1.75)	
	Medium	15	87	0.69 (0.38-1.23)	
	High	11	79	0.61 (0.31-1.19)	
Diffuse large cell (339 cases, 1,401 controls)	Background	298	1,171	1	0.07 / 0.02
	Low	15	64	0.83 (0.46-1.52)	
	Medium	14	87	0.54 (0.30-0.98)	
	High	12	79	0.56 (0.29-1.05)	
Small cell*** (137 cases, 1,401 controls)	Background	112	1,171	1	0.98 / 0.71
	Low	8	64	1.07 (0.48-2.40)	
	Medium	10	87	0.96 (0.47-1.98)	
	High	7	79	0.86 (0.37-1.98)	
Subgroups based on topography					
Nodal lymphomas*** (532 cases, 1,401 controls)	Background	444	1,171	1	0.81 / 0.87
	Low	30	64	1.26 (0.75-2.13)	
	Medium	34	87	1.09 (0.67-1.75)	
	High	24	79	0.93 (0.54-1.60)	
Extranodal lymphomas*** (262 cases, 1,401 controls)	Background	211	1,171	1	0.30 / 0.07
	Low	13	64	1.28 (0.64-2.55)	
	Medium	16	87	1.08 (0.58-2.04)	
	High	22	79	1.72 (0.96-3.07)	

*All analyses were adjusted for sex, five-year age group, sex by five-year age group, province, number of years worked from age 18, education, cigarette pack-years, work with pesticides or herbicides, occupational radiation exposure, and use of electric home heat.

** Test of trend for cumulative MF exposure based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous cumulative MF exposure index for the category in place of the categorical cumulative MF exposure variable.

*** Results may not be reliable due to quasi-complete separation and large number of large standard error (beta) in results.

Table 5.11 Risk of non-Hodgkin's lymphoma associated with occupational cumulative magnetic field exposure stratified by sex among 1,350 cases and 1,401 controls, NECSS, Canada 1994-1997*

Population (sample size)	Cumulative MF exposure	Cases	Controls	Odds ratios (95% CI)	P-value for heterogeneity / p-value for trend**
Primary analytic population (1,350 cases, 1,401 controls)	Background	1134	1171	1	0.53 / 0.42
	Low	74	64	1.10 (0.77-1.58)	
	Medium	71	87	0.80 (0.57-1.13)	
	High	71	79	0.92 (0.65-1.30)	
Males (705 cases, 728 controls)	Background	528	542	1	0.89 / 0.76
	Low	54	48	1.07 (0.70-1.62)	
	Medium	56	67	0.87 (0.59-1.29)	
	High	67	71	0.97 (0.67-1.41)	
Females (645 cases, 673 controls)	Background	606	629	1	0.36 / 0.14
	Low	20	16	1.22 (0.61-2.43)	
	Medium	15	20	0.62 (0.31-1.24)	
	High	4	8	0.52 (0.15-1.82)	

*All analyses were adjusted for sex, five-year age group, sex by five-year age group, province, number of years worked from age 18, education, cigarette pack-years, work with pesticides or herbicides, occupational radiation exposure, and use of electric home heat.

** Test of trend for cumulative MF exposure based upon entering in the model a single continuous variable with a value equal to the median value of the original continuous cumulative MF exposure index for the category in place of the categorical cumulative MF exposure variable.

CHAPTER 6
DISCUSSION

6.1 Summary and Interpretation of Study Results

6.1.1 Occupational Magnetic Field Exposure

No association between occupational exposure to power frequency magnetic fields (MF) and non-Hodgkin's lymphoma (NHL) risk was observed in this population-based case-control study, nor was a dose-response gradient in relation to cumulative exposure observed. Adjustment for potential confounding factors including employment status, socioeconomic factors, smoking history, work with benzene, work with pesticides, occupational exposure to radiation, and ever use of electric heat as a primary method of home heating (considered to be a component of residential MF exposure) did not change these results. The study is one of the largest to look at MF in relationship to NHL (1,624 cases and 1,643 controls).

Our results are consistent with those reported for three retrospective cohort studies which found no association between NHL occurrence and occupational MF exposure: the study of Sahl *et al*[124] of a cohort of workers at an electrical utility in California; the study of Theriault *et al*[113] of the combined cohorts of workers from each of three electrical utilities; and the study of Villeneuve *et al*[115] of the Ontario Hydro cohort of workers from the tri-utility study of Theriault. In each of these studies, no association between NHL occurrence and occupational MF exposure was observed. In contrast, Schroeder and Savitz[123] observed increased risks of NHL associated with the higher categories of cumulative MF exposure in their cohort study of electrical workers from five American electrical utilities.

In our subgroup analyses, no specific subtype of NHL was identified in which there was an increased risk of disease associated with occupational MF exposure. In addition, risk did not vary by nodal status of the NHL. In fact, for cases classified as intermediate- or high-grade lymphoma in the Working Formulation, the risk appeared to decrease with increasing cumulative exposure. This is contrary to the findings of the study of Schroeder and Savitz[123] which found higher risks for the subgroup of intermediate/high-grade lymphoma compared to the overall NHL case group.

In the analyses in which we assessed the risk of NHL associated with cumulative exposure in different exposure time windows or with different occupational MF exposure indices (all of which were based on time-weighted average exposures), no important differences from the primary analysis were noted. Our findings of similar risks of NHL in the analyses based upon cumulative exposure in differing time windows are consistent with those of the study Sahl *et al.*[124] They observed that the risk of lymphomas associated with cumulative exposure occurring in various ten-year time windows did not differ from the risk associated with career cumulative exposure; all relative risks were close to one. In contrast, in the study of Schroeder and Savitz,[123] the highest risk of NHL was observed for cumulative MF exposure occurring in the past 10-20 year time window. Our findings of similar risks associated with different exposure indices are consistent with those of Villeneuve *et al*[134] in their study of occupational exposure to MF and brain cancer. They found that the risk of brain cancer, particularly glioblastoma multiforme, was increased with MF exposure, regardless of the exposure index used.

The results of the various sensitivity analyses we carried out were not materially different from those of the primary analysis. In our study, because exposure history was obtained retrospectively without the benefit of reliable records, it was not

unexpected that subjects would have had some difficulty recalling all past jobs and details of these jobs, particularly job dates; and that, as a result, the occupational data were sometimes incomplete and/or inconsistent. In our primary analyses we excluded all subjects with incomplete or inconsistent job dates in their occupational history. In order to assess the possible bias that this approach may have introduced, we carried out various sensitivity analyses in which different approaches of dealing with the missing or inconsistent data were used. The similarity of these results with those of the primary analysis suggests the lack of significant bias due to the exclusion of subjects with incomplete or inconsistent job history data from the primary study population.

Finally, the analyses we carried out to assess the effect of taking into account the pairing process that we used in the selection of control subjects from the full National Enhanced Cancer Surveillance System (NECSS) study population control pool yielded results little different from those in which the pairing process was ignored. Because the controls used in our study were a sub-sample of the full NECSS control sample, selected by matching each case of NHL to a single control by sex and five-year age group, some analysts consider it necessary to take this pairing into account in the analysis. Others recommend that subjects with identical values for the matching variables be pooled. Thus, in order to account for the matching, we conducted analyses using conditional logistic regression based upon the pairs and based upon the sex by five-year age group strata. In each case, the results were similar to those of unconditional logistic regression with the terms for sex, five-year age group, and the sex by five-year age group interaction term included in the model.

6.1.2 Other Risk Factors

We identified an increased risk of NHL in association with self-reported work with pesticides (OR 1.3, 95% CI: 1.0, 1.6). This result is consistent with reports from the epidemiologic literature suggesting an association of NHL with herbicide (particularly 2,4-dichlorophenoxyacetic acid) and possibly other pesticide exposure. However, no details on specific pesticides used were available for our study.

The risk of NHL associated with occupational radiation exposure was not significantly increased, consistent with the general consensus in the epidemiologic literature that radiation is not associated with NHL occurrence. In addition, the risk of NHL was not associated with cigarette smoking, again in keeping with the results of the majority of studies in the literature pertaining to smoking and NHL.

We observed an increased risk of NHL in subjects who had worked compared to subjects who had never worked, and this risk increased with longer duration of work. This result is difficult to explain. It is unlikely to be due to confounding by other occupational factors, as the study was a community-based study in which subjects held a variety of jobs. However, it should be noted that this result was based upon small numbers of non-workers and was not statistically significant.

In terms of socioeconomic factors, no statistically significant associations were observed. The risk of NHL was lower for people with a higher level of education but higher for people with a higher level of income. However, there was a large number of missing values for the income adequacy variable and the pattern was not consistent within the levels of income. There was no indication that subjects who did not provide information on income were at a different risk for NHL than for those who did provide this information.

Interestingly, we observed an increased risk of NHL for subjects who reported the use of electric heat as a primary method of home heating in any residence occupied for one year or longer (OR 1.2, 95% CI: 1.0, 1.4). We included the ever use of electric heat in the home variable as a covariate in our model because we thought this may be an indication of MF exposure in the home, and thus may be a partial adjustment for confounding by residential exposure of the risk associated with occupational exposure. It, in fact, did not result in confounding but did appear to be an independent factor in determining NHL risk. We are unable to explain this observation; ever use of electric home heat may be a surrogate for another exposure or the association may be a spurious finding. We consider the observed association unlikely to be due an increased risk of NHL associated with increased residential exposure to MF, because: a) we did not see an association with occupational exposure; and b) our measure was a crude incomplete measure of residential exposure.

6.2 Strengths and Limitations of the Study

6.2.1 Strengths

Our study had a number of strengths that are important to take into account in the interpretation of the negative findings for the risk of NHL associated with occupational MF exposure.

Our study was based on a large number of incident cases of histologically confirmed NHL and a large number of controls, providing good power to detect an effect if one were present. As we had incident cases rather than decedent cases, factors that affect prognosis rather than incidence will not appear to be risk factors for disease. Histological confirmation lessens the chance of bias due to disease misclassification. In

addition, the information available on both the histology and topography of the tumors, together with the large number of cases overall, allowed us to carry out subgroup analyses by both histology and topography.

As the study sample was population-based, there was less opportunity for selection bias in comparison with case-control studies with other study bases. In addition, MF exposures of subjects in study populations that are based on the general working population are likely to be more diverse than those of subjects in study populations based on single occupations or single industries, as is often the case in cohort studies.[2 (p. 114)] Furthermore, occupations with higher levels of MF exposure within a general population are less likely to be associated with other occupational exposures than are occupations with higher levels of MF exposure within a cohort defined by a single industry, making confounding by unknown occupational factors (such as a particular chemical or other such occupational exposures) less likely.

Assessment of the MF exposure for each of the individual jobs held by subjects was carried out by an expert in the area of electromagnetic fields. These assessments were done on a job-by-job basis with the expert blinded to the case/control status of the subject. Expert-assessed exposure has been shown to be reliable in the ranking of MF exposures. As reported by Bracken *et al*,[45] Loomis *et al* found agreement (statistics not reported) between the ranking of exposures as low, medium, or high by a panel of experts on the basis of job title and the results of eight-hour personal exposure measurements in their study of 134 utility workers. The method of exposure assessment used in our study was more reliable than that used in the earlier studies where exposure assessment was based upon an intuitive assessment that electrical jobs, such as electricians and radio operators involve higher levels of electromagnetic field

exposure. In addition, we consider the assessment of jobs on an individual basis to be more reliable than the assessment of jobs based on job exposure matrices in which similar jobs are grouped together into categories. The jobs grouped within these categories, although similar, may have varying exposures.

It is also important to note that significant associations were demonstrated in the earlier study of Villeneuve *et al*[134] of brain cancer and occupational MF exposure. This study used the same method for MF job exposure assessment as in our study; and was based on the case-control component of the NECSS as was our study. In this study, an increased risk of glioblastoma multiforme (OR 5.4, 95% CI: 1.2, 25) among men who ever held a job with MF exposure 0.6 μT or higher relative to those who held jobs only with background levels of exposure (<0.3 μT) was found. Furthermore, the cumulative MF exposure index (treated as a continuous variable) was significantly related to gliobastoma multiforme risk (p=0.02). These results suggest that our study should have had sufficient sensitivity to demonstrate an effect of MF on NHL risk if one were present.

Another strength of our study was the availability of information for the complete occupational history of subjects, including information on job title, industry, and duties as well as job dates, obtained directly from subjects by questionnaire. This allowed us to: assess the effect of cumulative exposure rather than simply ever/never exposure; assess the effects of exposure in different time windows; assess the effects of exposure as measured by different indices; and make more accurate assessments of MF exposure than those in some earlier studies. In some of the earlier studies, information on occupation was available only from census information or death certificates, and only for the most recent job. These sources of data can lead to exposure misclassification because of their lack of reliability and because past jobs are not taken into

consideration. In addition, they can also lead to misclassification because job site is not taken into account. For example, Miller *et al*[125] found in the creation of their job exposure matrix for male employees of Ontario Hydro that some workers (such as professionals, managers, clerks, and storekeepers) with expected low exposure actually had high exposure if they worked in a site (such as hydroelectric stations and transformer stations) with high general exposure.

Although cumulative exposure was chosen to be our primary index of the time-weighted average exposure to MF, cumulative exposure and other indices incorporating duration of exposure can sometimes be misleading measures. As noted by Savitz *et al*[128] "a late-stage effect might not show increasing risk with increasing duration of exposure if there were a immediate response by 'susceptibles', with those less vulnerable surviving to have a more prolonged exposure". For example, for carcinogens acting at a late stage, early exposure may modify the effect of more recent exposure, in that only those subjects who had no early exposure are at risk for effects from the more recent exposure. Alternatively, if MF is acting as a late promoting or progression agent only after initiation of cells by other factors, the effects of the more recent MF exposure may be the only relevant exposure in the causation of disease. We did consider time windows of exposure in our analyses, although we did not adjust the effect of exposure in a particular time window for the effects of exposure in other time windows.

Finally, a major strength of the study was the availability of data for a number of potential confounding factors including: smoking history; socioeconomic factors; and exposures through work to benzene, pesticides, and ionizing radiation.

6.2.2 Limitations

Although the study had a number of strengths, it also had some limitations. Despite the inclusion of a large number of cases and controls, the number of subjects exposed to MF above background levels was not large. This reduced the power to detect an effect if one were present and resulted in lower precision of our risk estimates. Furthermore, of those subjects with exposures above background, many did not have high exposures for prolonged periods of time. Thus, in our study, we were exploring effects at the lower end of any dose-response curve.

Although the NECSS case-control component was population-based, it is likely that some selection biases occurred. Firstly, cases that died within four months of diagnosis were not recruited into the study population. Thus the more aggressive cases of NHL were likely excluded. This is supported by the observation that the proportion of high-grade lymphomas in our case series was lower than expected from population data (i.e., 5% in our series versus 17% reported in the literature).[49] If the aggressive and more rapidly fatal cases had a different etiology from cases with longer survival or if MF exposure affects prognosis rather than etiology, the fact that the aggressive cases were excluded would have resulted in a bias in our results. Secondly, non-response for both cases and controls was moderately high. It is possible that factors associated with non-response varied by case/control status.

Bias in the selection of controls may also have occurred. In the provinces in which controls were selected through random digit dialing, people without phones were not represented (estimated at less than 2%) while people who are often at home were likely over represented. In the provinces in which controls were selected through the

use of health files, the approximately 5% of the population that is covered by other plans (e.g., First Nations, federal military, and RCMP) were excluded.

Although we had information on histology and topography, the classification of NHL cases by subtype or nodal status was not always straightforward. The histology was coded using terms for NHL from more than one classification scheme, which made it difficult to translate the codes to a common scheme. For a large number of cases the coding of histology was too nonspecific to allow for classification by subtype. In addition, nodal status was not always clear-cut. Although pathology should be coded based on the location of the primary tumor rather than the site of biopsy, it was apparent that this was not always done because for many cases the topography codes indicated bone marrow or blood as the location of the tumor. Furthermore, NHL is often a systemic disease at the time of presentation, making it difficult to know the site of origin.

While our exposure assessment was based upon the subject's complete occupational history and assessment by an expert of MF exposure in each job, these assessments were not based on direct measurements and thus may be considered less reliable than exposure assessments that are based on direct measurements. In addition, the job MF exposures were categorized in a semi-quantitative fashion. Thus our cumulative estimates were based upon these semi-quantitative exposure categories, which limited the amount of quantitative information, and also made it difficult to compare our results directly with the results of other studies that used quantitative measures.

Residential exposure to MF, other than that measured by the use of electric home heat, and other sources of exposure to MF were not taken into account. Bias as a

result of either measurement error or confounding can occur in epidemiologic studies due to the lack of consideration of exposure from other sources. As discussed by Loomis and Savitz,[148] if one is primarily interested in measuring the association between exposure and outcome (as we were), then taking into consideration only one source of exposure constitutes measurement error. If one is more interested in evaluating a particular source of exposure, for example occupational sources for setting work standards, the unmeasured component can lead to confounding of the association between exposure and outcome. Although non-differential exposure measurement error will generally result in biasing the relative risk toward the null, if the unmeasured exposure varies with the measured component of exposure (yet is not related to disease status), the relative risk can be biased upward or downward depending upon the relationship between the two components. It is possible that the measured occupational exposure was correlated with unmeasured non-occupational exposure in our study. For instance, if workers in jobs at the highest level of exposure tended to work at these jobs for shorter time periods than workers in jobs at the mid level of exposure, then the unmeasured component of cumulative exposure would be greater for workers in the jobs with the highest exposure than that for those working for longer periods of time in jobs at the mid level of exposure.

Furthermore, it is possible that characteristics of electromagnetic fields associated with electricity other than those captured by the time-weighted average MF are more relevant to the cancer etiology. In our study, we did not have information on other exposure metrics, such as time spent above a threshold or rate of change, for the MF exposure; and we had no information on electric field exposure. In the study of Villeneuve *et al*[115] of NHL in electric utility workers in Ontario, electric field exposure,

particularly exposure above a threshold, was associated with NHL risk while MF exposure generally was not. In addition, it has been shown that various indices of electric field exposure are poorly correlated with indices of MF exposure in these electrical utility workers.[149]

Although we had data on many factors to control for potential confounding, the data for some factors were either not always complete or not considered reliable. For example, there was a large number of missing values for income adequacy, as is common in many epidemiologic studies. Further, data on work with either benzene or pesticides were based upon self-report. In our data, there was little correlation between self-reported exposure to radiation sources at work and exposure of greater than 1 mSv per year based on an expert assessment of the subject's occupational history (results not presented). In a case-control study in males in Montreal in which self-reported exposure to occupational substances was compared with expert-assessment, it was found that the sensitivity of self-assessment as compared to expert-assessment was low. In fact, the authors concluded that "self-reports are not sufficiently accurate to warrant their sole use in population-based studies, although in certain situations their use might be justifiable."[150] In addition, in regard to self-reported work with pesticides, it was unclear subjects' interpretation of the two questions regarding pesticides and herbicides, given that 46 subjects reported having worked with herbicides but not pesticides while the scientific definition of pesticides ("substances used to prevent, destroy, repel or mitigate any pest ranging from insects, animals and weeds to microorganisms such as fungi, molds, bacteria and viruses"[151]) includes herbicides as a specific type of pesticide.

In addition, we did not have data available on some of the established risk factors for NHL (immunosuppression and viral causes) in order to control for potential confounding. Although it is likely that there is a negative association between poor health and work with higher levels of MF exposure, the risk factors for NHL associated with immunosuppression are not common. The viral factors, while common, are considered to be unlikely to be highly associated with occupational exposure to MF. In addition, in our study it was observed that workers in general had a greater risk of NHL. Therefore we consider it unlikely that these factors caused significant confounding of the NHL-MF association.

Because occupational data were obtained retrospectively from subjects, there was a relatively large amount of missing and/or inconsistent information. Our general approach was to omit subjects with these missing or inconsistent data from the analyses. As this involved a relatively large number of subjects, it is possible that some bias was introduced. However, various sensitivity analyses did not confirm this. In addition, we were also missing data for income for over a quarter of subject, and we were not able to include this variable in our main analyses. Exclusion of subjects due to missing data for the other variables of interest resulted in the loss of only a small number of subjects.

Our study was a case-control study while most to the more recent studies have been cohort studies. Although both study types are valid, case-control studies can be more prone to bias. For example, recall bias, which was possible in our case-control study, does not occur in cohort studies. It is possible that cases may have completed the detailed occupational questions in the questionnaire more carefully than controls. However, it is unlikely that they over-reported jobs with MF exposure as cases would not

have been aware of the hypothesis that MF may increase the risk of NHL. In addition, because our case-control study was not based on incident density sampling, we were unable to study temporal aspects and adjust for effects related to the healthy worker effect as well as can be done in a cohort study or a case-control study with such control sampling.

Furthermore, it should be noted that there are limitations common to all types of epidemiologic studies of NHL risk related to occupational MF exposure. These are outlined in the next section.

6.3 Limitations of Studies of Occupational Exposure to Magnetic Fields and Non-Hodgkin's Lymphoma

Epidemiologic studies in which the goal is to identify the risk of NHL associated with occupational exposure to MF are difficult to carry out and to interpret for a number of reasons.

First, if MF does cause cancer, it is possible that the risk is not very high. Small risks or larger risks in small subgroups, although important, are difficult to detect in epidemiologic studies. In addition, there is no unexposed group, as everyone is exposed to these fields in modern life, making the variation in exposure across the population small, and the risk therefore more difficult to detect.

Second, exposure assessment is problematic. It is likely that significant exposure misclassification occurs in all studies, and that it often results in bias toward a null result. There is day-to-day variation in exposure to individual workers as well as variation between workers within the same occupational category.[45] Exposures are generally based upon measurements taken in the current environment, and exposures can change over time with changes in work practices or changes in current load

exposures. Dosimeters can be useful but workers may modify their behaviours and possibly their exposures when wearing dosimeters or when participating in a study.[128] Exposures are not generally remembered by individuals and thus cannot easily be detected by questionnaire. Each of these factors would likely lead to non-differential exposure misclassification and thus lead to a bias toward a null result.

Third, the appropriate dose metric and temporal relationship between exposure and outcome are not known.[124] Because alternating MF are complex physical entities with numerous characteristics, there are various aspects that can be measured (such as average strength, peak strength, rate of change, and field orientation). Exposure measures used may miss the biologically relevant attributes of MF, although examination of occupational exposures has indicated that many MF metrics are to some extent related. Thus high measures for time-weighted average exposure (the most commonly used metric) are correlated to some degree with high measures for other, potentially more relevant, metrics.[152] It is also possible that electric field exposure is the more relevant exposure. Electric and magnetic field exposure indices have been shown to be only weakly correlated with one another.[153] In addition, because temporal relationships between exposure and outcome are unknown, results may be diluted by combining relevant exposure time windows with non-relevant exposure windows in cumulative measures.[124]

Fourth, occupational studies ignore the possible contribution of other exposures. In occupational studies it is necessary to assume that occupational exposures are higher than other exposures and that the timing of exposure and circadian effects are unimportant.

Fifth, NHL is a heterogeneous disease, and different subtypes may have different etiological factors. Sub-type specific associations may be missed when NHL is treated as a single entity.[123] However, as NHL is not common, the number of cases available for study is usually not large, which precludes carrying out analyses based upon subtypes with any precision. In addition, subtypes of NHL can be difficult to define and to identify. For instance, as summarized by Groves *et al*,[12] agreement among expert pathologists in classifying NHL according to the Working Formulation was only about 60% and agreement among Surveillance, Epidemiology, and End Results (SEER) Program coders in assigning the International Classification of Diseases-Oncology (ICD-O) codes to cases was 77%. Further, lymphomas are sometimes coded without specific histological information. As reported by Herrinton,[154] reviewers of the SEER cancer statistics from 1982 to 1992 found that approximately 20% of the NHL cases were termed 'unclassified lymphoma'. She speculated that "this classification may indicate: 1) poor pathologic material; 2) an ambiguous tumor; 3) an inadequate classification system; or 4) the absence of a compelling reason (or the lack of resources) to obtain detailed histologic or immunophenotypic information about a neoplasm." Further complicating the issue, there are several classification schemes in current and/or past use.

Last, the etiology of NHL is for the most part unknown. This makes uncontrolled confounding impossible to rule out.[123] Exposure of electrical workers to MF may be associated with occupational exposure to other environmental chemicals, radon, or ionizing radiation. In addition, an association between higher exposure and good health could exist and result in confounding leading toward null results.[124]

6.4 Conclusions and Recommendations

6.4.1 Conclusions

Our results provide no support for the hypothesis that MF exposure is a causal factor for NHL. In addition, while there are a small number of studies within the epidemiologic literature that suggest a potential effect of MF exposure on NHL occurrence, the majority of the reports do not support such an effect. However, due to the limitations in the studies carried out to date (including our own), we also believe the possibility of an effect cannot be totally ruled out.

In addition, based on our study results and review of the epidemiologic literature, we conclude that there is evidence for an association between NHL and pesticide exposure, but no strong evidence for an association between NHL and either smoking or ionizing radiation exposure.

6.4.2 Recommendations

It may prove impossible to answer definitively the question regarding carcinogenicity of MF using epidemiologic studies. Because of the limitations noted earlier that are common to most, if not all, epidemiologic studies in this area, more research is required in the laboratory before epidemiology can progress. It is vital to determine the correct exposure metric and the relevant etiologic time window. In addition, it is also considered important to conduct studies in which all sources of exposure are taken into account. Furthermore, epidemiologic studies would best be conducted in populations with complete registers and records in order to reduce the possibility of selection bias and information bias which are difficult to overcome in many of the studies conducted to date.

In order to determine the cause of the increasing incidence of NHL other potential environmental risk factors should be explored. In addition, the heterogeneous nature of NHL should be taken into account; histology and topography should be considered in the risk assessments for alternative hazards.

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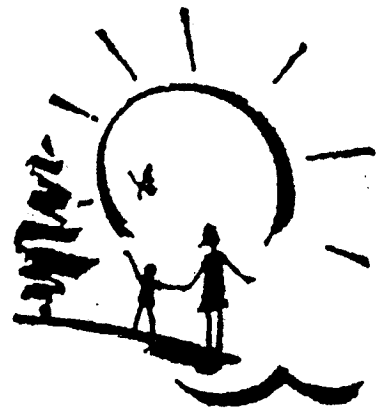
APPENDIX 1
THE NATIONAL ENHANCED CANCER SURVEILLANCE SYSTEM QUESTIONNAIRE

Health Canada Santé Canada



Environmental Health Survey

(Confidential when completed)

ID Number
First name/Middle name/Last name
Mailing Address: Street and Number/P.O. Box No.
Town/Province
Postal Code

Guide to filling in this Questionnaire:

Please choose answers by:
completely filling in the circle; ○ → ●

writing in the boxes; [ ] → [8,9]

or filling in the blank spaces provided. *April*

This form asks a variety of questions about you and your environment, which may affect or be related to your health. The information you provide will help Canadians to understand more about preventing disease.

Please complete each question as best you can even if you are not sure of your answer.

You do not need to fill in the entire questionnaire all at once. You may wish to take a brief rest in the middle.

If you have any questions about the survey or would like help filling it out, please call

_____

at _____ .

Please return this questionnaire by

☐ **Si vous préférez répondre en français, veuillez cocher la case et renvoyer le questionnaire dans l'enveloppe adressée ci-jointe.**

GENERAL INFORMATION

1. Today's date _____ / Month / Day / Year

2. **Is anyone helping you** (the person whose name appears on the front of the questionnaire) to complete this questionnaire?
   - o No
   - o Yes → o Spouse
   - o Other -- Please specify: _____

3. When were you born?
   _____ / Month / Day / Year

4. Are you
   - o Female
   - o Male

5. **To which ethnic or cultural group(s) did your ancestors belong?**

   Mark or specify as many as applicable.

   - o French
   - o English
   - o German
   - o Scottish
   - o Italian
   - o Irish
   - o Ukrainian
   - o Chinese
   - o Dutch
   - o Jewish
   - o Polish
   - o Black
   - o Aboriginal
   - o Métis
   - o Inuit
   - o Other ethnic or cultural group(s) -- Please specify: _____

   Examples of other ethnic or cultural groups are: Portuguese, Greek, Indian, Pakistani, Vietnamese, Japanese, Lebanese, Haitian, etc.

6. What is your **marital** status?
   - o Single
   - o Married
   - o Common law
   - o Widowed
   - o Divorced/Separated
   - o Other

7. What is the **highest grade** (or year) of high school or elementary school that you have completed?
   Grade ☐☐ o Never attended school

8. How many years of post-secondary school have you completed?
   ☐☐ years o none

9. Have you smoked **at least 100 cigarettes** in your entire life?
   - o No → Go to 10
   - o Yes

   About how old were you when you **first started** smoking cigarettes? ☐☐ years old

   About **how many years** in total did you smoke ? ☐☐ years

   Of the entire time you smoked, how many **cigarettes**, on the average, did you smoke **per day**? ☐☐ per day

   Do you smoke cigarettes now?

   - o No → How old were you when you **stopped** smoking? ☐☐ years old
   - o Yes → On the average, about how many **cigarettes a day** do you smoke now? ☐☐ per day

10. Have you ever smoked a **pipe or cigars** regularly?
    - o No → Go to 11
    - o Yes

    For how many years? ☐☐ years
    About how many pipes or cigars? ☐☐ per day or ☐☐ per week

11. Have you ever used **chewing tobacco** regularly?
    - o No → Go to 12
    - o Yes

    For how many years? ☐☐ years
    About how many plugs? ☐☐ per day or ☐☐ per week

12. How **tall** are you?
    ☐ feet ☐☐ inches or ☐☐☐ centimetres

13. How much did you **weigh** about 2 years ago?
    ☐☐☐ pounds or ☐☐☐ kilograms

14. What is the **most you have ever weighed?** (Women should not include pregnancy.)
    ☐☐☐ pounds or ☐☐☐ kilograms

RESIDENTIAL HISTORY

15. Please list each of the places **in Canada** you have lived for at least **1 year.** Start with the most recent residence and follow back to your childhood. (If you cannot remember exact details, provide your best recollection, for example, nearest cross-street or intersection.)

	TIME PERIOD	ADDRESS			
	First Year *Last Year*	Street and Number or Lot, Concession and Township **(If you don't remember the exact address, give the nearest cross-street or intersection.)**	City, Town, or Municipality	County or District, if rural	Province
	Example: 19 8 9 to 19 9 3	*97 Greargate Rd.*	*Brandon*		*Manitoba*
1	19 ☐☐ to 19 ☐☐				
2	19 ☐☐ to 19 ☐☐				
3	19 ☐☐ to 19 ☐☐				
4	19 ☐☐ to 19 ☐☐				
5	19 ☐☐ to 19 ☐☐				
6	19 ☐☐ to 19 ☐☐				
7	19 ☐☐ to 19 ☐☐				
8	19 ☐☐ to 19 ☐☐				
9	19 ☐☐ to 19 ☐☐				
10	19 ☐☐ to 19 ☐☐				
11	19 ☐☐ to 19 ☐☐				
12	19 ☐☐ to 19 ☐☐				

ADDRESS	Main source of **drinking water**						Primary types of **home heating** (Mark those which apply.)							Were you aware of **dusts or odours from industry** while living at this residence?				How many **regular smokers** usually lived in this home with you?				
Postal Code	Town/city water	Dug well	Drilled well	Bottled	Other	Don't know	Oil	Natural gas/propane	Electric	Wood	Coal	Other	Don't know	Never	At least once a month	At least once a week	At least once a day	None	1	2	3 or more	Don't know
R7A 8A7	●	○	○	○	○	○	○	○	●	○	○	○	○	○	○	●	○	○	○	○	●	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

EMPLOYMENT HISTORY

16. Please tell us about **each job you had for at least 12 months in Canada or elsewhere.** Include seasonal work, part-time, etc., if you worked the equivalent of 12 months or more. Begin with your most recent job and continue back to your first job. Please estimate the time period if you cannot remember exact years. (Even if you have retired, we still require the information.)
If you have never been employed, check here ☐ and continue to Question 17.

	TIME PEROID *First Year* *Last Year*	Type of Industry, Business, or Service and Company Name	Main Job Duties
	Example: 19 8 9 to 19 9 3	*Oil industry, Bluestar Oil Company*	*Process powerhouse and sulphur plant operations.*
1	19 ☐☐ to 19 ☐☐		
2	19 ☐☐ to 19 ☐☐		
3	19 ☐☐ to 19 ☐☐		
4	19 ☐☐ to 19 ☐☐		
5	19 ☐☐ to 19 ☐☐		
6	19 ☐☐ to 19 ☐☐		
7	19 ☐☐ to 19 ☐☐		
8	19 ☐☐ to 19 ☐☐		
9	19 ☐☐ to 19 ☐☐		
10	19 ☐☐ to 19 ☐☐		

Job Location(s) *City/town and province*	Job Title	Status *Full time / Part time / Seasonal / Other*	At this workplace, were you aware of **dusts or odours** from industry? *Never / At least once a month / At least once a week / At least once a day*	About how many people **smoked regularly** in your **immediate** work area? *None / 1 or 2 / 3 to 5 / 6 or more / Don't kn*
Rocky Mountain House, Alberta	*Gas plant operator*	● ○ ○ ○	○ ○ ○ ●	○ ○ ○ ● ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○

17. Have you ever worked with any of the following **for more than one year?**

	Never	Don't know	At work	At home	How many years in total?
Asbestos	o	o	o	o	
Arsenic salts	o	o	o	o	
Chromium salts	o	o	o	o	
Cadmium salts	o	o	o	o	
Coal tar, soot, pitch, creosote, asphalt	o	o	o	o	
Mineral, cutting or lubricating oil	o	o	o	o	
Benzidine	o	o	o	o	
Benzene	o	o	o	o	
Isopropyl oil	o	o	o	o	
Dyestuffs	o	o	o	o	
Vinyl chloride	o	o	o	o	
Pesticides	o	o	o	o	
Herbicides	o	o	o	o	
Mustard gas	o	o	o	o	
Radiation sources	o	o	o	o	
Welding	o	o	o	o	
Wood dust	o	o	o	o	

You are more than halfway through the questionnaire. This is a good place to take a short break, if you wish.

DIET INFORMATION

18. During the past 20 years have you ever taken any of the following vitamin or mineral supplements?

Vitamin and Mineral type	How often?			For how many years in total?					
	No	Yes, but not regularly	Yes, fairly regularly	Less than 1 year	1 to 2 years	3 to 5 years	6 to 9 years	10 to 19 years	20 + years
Multiple vitamins	o	o	o	o	o	o	o	o	o
Vitamin A	o	o	o	o	o	o	o	o	o
Beta-carotene	o	o	o	o	o	o	o	o	o
B-complex vitamins	o	o	o	o	o	o	o	o	o
Vitamin C	o	o	o	o	o	o	o	o	o
Vitamin E	o	o	o	o	o	o	o	o	o
Calcium	o	o	o	o	o	o	o	o	o
Iron	o	o	o	o	o	o	o	o	o
Zinc	o	o	o	o	o	o	o	o	o
Selenium	o	o	o	o	o	o	o	o	o

19. This section asks about your eating habits **about two years ago.** We ask you to mark the column best describes how often you ate or drank each of the following foods and beverages at that time.

	Never or less than 1 per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6 pe da
BEVERAGES MADE WITH WATER									
Coffee (1 cup)	o	o	o	o	o	o	o	o	o
Tea (1 cup)	o	o	o	o	o	o	o	o	o
Orange or grapefruit juice from frozen concentrate (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Other juices or drinks from frozen concentrate (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Drinks from powdered drink crystals (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Tap water (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
Bottled water (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
OTHER BEVERAGES									
Whole milk (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
2% milk (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
1% milk (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
Skim milk (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
Orange or grapefruit juice, fresh, bottled or canned (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Other juices or drinks, fresh, bottled or canned (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Tomato or vegetable juices (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Soft drinks (1 glass/bottle/can)	o	o	o	o	o	o	o	o	o
Beer (1 bottle/can)	o	o	o	o	o	o	o	o	o
Wine (1 glass)	o	o	o	o	o	o	o	o	o
Liquor (1 drink or shot)	o	o	o	o	o	o	o	o	o

(continuea

19. (continued) Please mark the column that best describes how often, on average, you ate these foods **about two years ago.**

	Never or less than 1 per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6 + per day
FRUIT									
Apples or pears (1)	o	o	o	o	o	o	o	o	o
Oranges (1)	o	o	o	o	o	o	o	o	o
Bananas (1)	o	o	o	o	o	o	o	o	o
Cantaloupe (¼ melon)	o	o	o	o	o	o	o	o	o
Other fruit, fresh or canned (1 piece or ½ cup)	o	o	o	o	o	o	o	o	o
VEGETABLES									
Tomatoes (1 or ½ cup)	o	o	o	o	o	o	o	o	o
Carrots (1 whole or ½ cup)	o	o	o	o	o	o	o	o	o
Broccoli (½ cup)	o	o	o	o	o	o	o	o	o
Cabbage, cauliflower, brussels sprouts (½ cup)	o	o	o	o	o	o	o	o	o
Spinach or other greens (1 serving)	o	o	o	o	o	o	o	o	o
Yellow (winter) squash (½ cup)	o	o	o	o	o	o	o	o	o
Any other vegetable including green beans, corn and peas (½ cup)	o	o	o	o	o	o	o	o	o
Soups with vegetables (1 cup)	o	o	o	o	o	o	o	o	o
Potatoes: baked, boiled (1) or mashed (1 cup)	o	o	o	o	o	o	o	o	o
French fries or fried potatoes (½ cup)	o	o	o	o	o	o	o	o	o
Sweet potatoes (1 or ½ cup)	o	o	o	o	o	o	o	o	o
Tofu or soybeans (3-4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Baked beans or lentils (½ cup)	o	o	o	o	o	o	o	o	o
BREADS AND CEREALS									
Bran or granola cereals, shredded wheat (1 cup)	o	o	o	o	o	o	o	o	o
Other cold cereals (1 cup)	o	o	o	o	o	o	o	o	o
Cooked cereals (1 cup)	o	o	o	o	o	o	o	o	o
White bread (1 slice) or rolls (1)	o	o	o	o	o	o	o	o	o
Dark or whole grain bread (1 slice) or rolls (1)	o	o	o	o	o	o	o	o	o
Rice (1 cup)	o	o	o	o	o	o	o	o	o
Macaroni, spaghetti or noodles (1 cup)	o	o	o	o	o	o	o	o	o

(continued)

19. (continued) Please mark the column that best describes how often, on average, you ate these foods **about two years ago.**

	Never or less than 1 per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6 + per day
MEAT, POULTRY, FISH, EGGS & CHEESE									
Chicken or turkey (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Beef, pork or lamb as a main dish (steak, roast, ham) (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Beef, pork or lamb as a mixed dish (stew or casserole, pasta dish) (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Hamburger (1)	o	o	o	o	o	o	o	o	o
Hot dogs (1)	o	o	o	o	o	o	o	o	o
Luncheon meats (salami, bologna) (1 piece or slice)	o	o	o	o	o	o	o	o	o
Smoked meat or corned beef (1 piece or slice)	o	o	o	o	o	o	o	o	o
Bacon (1 slice)	o	o	o	o	o	o	o	o	o
Sausage (1)	o	o	o	o	o	o	o	o	o
Liver (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Fish, fresh, frozen or canned (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Fish, smoked, salted or dried (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Eggs (1)	o	o	o	o	o	o	o	o	o
Cheese other than cottage cheese (1 slice or 1 oz)	o	o	o	o	o	o	o	o	o
SWEETS									
Cake (1 slice)	o	o	o	o	o	o	o	o	o
Cookies (1)	o	o	o	o	o	o	o	o	o
Doughnuts, pastry (1)	o	o	o	o	o	o	o	o	o
Pies (1 slice)	o	o	o	o	o	o	o	o	o
Ice cream (½ cup)	o	o	o	o	o	o	o	o	o
Chocolate (1 small bar or 1 oz)	o	o	o	o	o	o	o	o	o
MISCELLANEOUS									
Potato chips (small bag or 45g)	o	o	o	o	o	o	o	o	o
Peanut butter (1 tbsp)	o	o	o	o	o	o	o	o	o
Nuts (1 oz/30g)	o	o	o	o	o	o	o	o	o
Margarine on bread or vegetables (1 pat or tsp)	o	o	o	o	o	o	o	o	o
Butter on bread or vegetables (1 pat or tsp)	o	o	o	o	o	o	o	o	o
Mayonnaise or salad dressing on bread or in salads (1 tbsp)	o	o	o	o	o	o	o	o	o

20. About two years ago:

	Seldom or Never	Sometimes	Often or Always
How often did you **add salt** to your food?	o	o	o
How often did you **add pepper** to your food?	o	o	o
How often did you have **onions or garlic** in your food?	o	o	o
How often did you **eat the skin on chicken**?	o	o	o
How often did you **eat the fat on meat**?	o	o	o

21. What kinds of **fat did you usually use** in cooking about 2 years ago?
Mark only 1 or 2.

- o Block or stick margarine
- o Soft tub margarine
- o Low-calorie margarine
- o Shortening
- o Butter
- o Oil
- o Lard, baconfat, fatback
- o Non-stick spray or no fat
- o Don't know or don't cook

22. What kinds of **fat did you usually put** on bread, potatoes and vegetables about 2 years ago?
Mark only 1 or 2.

- o Block or stick margarine
- o Soft tub margarine
- o Low-calorie margarine
- o Butter
- o Cream cheese
- o Didn't add fat

23. Summary Questions

About 2 years ago:

	Never or less than 1 per month	Less than 1 per week	1 to 2 per week	3 to 4 per week	5 to 6 per week	1 per day	1½ per day	2 per day	3 per day	4 + per day
How often did you use **fat or oil in cooking**?	o	o	o	o	o	o	o	o	o	o
Not counting salad or potatoes, **how many servings of vegetables** did you eat?	o	o	o	o	o	o	o	o	o	o
Not counting juices, how many **servings of fruit** did you eat?	o	o	o	o	o	o	o	o	o	o
How often did you eat **fried food** from a **restaurant or take-out**? (for example, french fries, fried chicken, fried fish)	o	o	o	o	o	o	o	o	o	o

24. We have a few questions about your **usual eating habits 20 years ago.** What you have just told us about the different places you have lived and worked might help in remembering back to your eating habits at that time.

For each of the following foods and beverages, please indicate **whether you usually ate or drank more or less 20 years ago** than you did about 2 years ago. Please mark the appropriate column for each food or beverage.

Compared to 2 years ago, 20 years ago I used to consume:	Much less	Some-what less	About the same amount	Some-what more	Much more
Beef, pork or lamb	o	o	o	o	o
Chicken or fish	o	o	o	o	o
Milk	o	o	o	o	o
Vegetables	o	o	o	o	o
Fruit	o	o	o	o	o
Bread	o	o	o	o	o
Margarine	o	o	o	o	o
Butter	o	o	o	o	o
Fried foods	o	o	o	o	o
Sweets	o	o	o	o	o
Tea	o	o	o	o	o
Coffee	o	o	o	o	o
Soft Drinks	o	o	o	o	o
Alcohol	o	o	o	o	o

25. About **how many times** have you gone on a **diet to lose weight** during your adult life?

- o Never
- o 1 to 2 times
- o 3 to 5 times
- o 6 to 8 times
- o 9 to 11 times
- o 12 or more times

PHYSICAL ACTIVITY

26. About 2 years ago, how often did you do the following activities, on average?

	Which seasons?					How often?					Time per session			
	Never	Spring	Summer	Fall	Winter	Less than 1 per month	1-3 per month	1-2 per week	3-6 per week	Every day	Less than 15 minutes	15-30 minutes	31-60 minutes	60+ minutes
Walking for exercise	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Jogging or running	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Gardening or yard work	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Home exercises or exercise class	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Golf	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Tennis or squash	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Bowling or curling	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Swimming or water exercises	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Skiing or skating	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Bicycling	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Social dancing	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Other strenuous exercise	o	o	o	o	o	o	o	o	o	o	o	o	o	o

OTHER GENERAL INFORMATION

27. What was the **approximate total income for all household members** from all sources, **before income taxes,** in an average year during the last 5 years?

- o less than $10,000
- o $10,000 - $19,999
- o $20,000 - $29,999
- o $30,000 - $49,999
- o $50,000 - $99,999
- o greater than $100,000
- o prefer not to answer

28. How many members are there in your household in total?

☐ persons

WOMEN:
Please continue to the next page.

MEN:
You have now completed the questionnaire.

Please take a moment to fill in any questions you may have missed.

THANK YOU VERY MUCH
for taking the time to fill out this questionnaire. Your participation is sincerely appreciated.

Please return this completed questionnaire in the self-addressed envelope.

QUESTIONS FOR FEMALES ONLY

MENSTRUATION

29. How old were you when you had your first menstrual period?

    ☐ years old
    o Don't remember
    o Haven't menstruated → Go to 33

30. Between the ages of 10 and 30, did your menstrual periods tend to occur regularly or irregularly (menstrual cycles varied by more than 10 days in length)? Please exclude any time when you were pregnant or using birth control pills.

    o Regularly o Irregularly

31. **How old** were you when you had your **last menstrual period**?

    ☐ years old
    o Still menstruate → Go to 33

32. How did your **menstrual periods stop**?
    o Naturally--that is, as part of the change of life
    o As a result of a hysterectomy (removal of womb)
    o Following radiation
    o Other -- Please specify:

    _____

33. Have you had an operation to remove **BOTH your ovaries**?
    o No
    o Yes → At what age? If they were removed on two separate occasions, record when your second ovary was removed.
    At age ☐ years

34. Do you have **mammograms** (x-rays of the breast) performed on a **routine** basis (every two years)?
    o No
    o Yes → First mammogram at age ☐ years

PREGNANCIES

35. Have you ever been pregnant?
    o No → Go to bottom of page.
    o Yes

36. **How many times have you been pregnant?** Include live births, stillbirths, miscarriages, abortions and ectopic (tubal) pregnancies.
    ☐ times

37. How old were you at the end of your first **pregnancy**?

    ☐ years old

38. How many **of your pregnancies** were live births?
    ☐ live births o none

39. How old were you at the end of your first pregnancy which lasted 5 months or more?
    ☐ years old

40. For how many **months** in total did you **breastfeed**? (Add the number of months that you breastfed after each birth to give the total number of months.)
    ☐ months o never breastfed

Please take a moment to fill in any questions you may have missed.

THANK YOU VERY MUCH for taking the time to fill out this questionnaire. Your participation is sincerely appreciated.

Please return this completed questionnaire in the self-addressed envelope.

APPENDIX 2
TABLES OF VARIABLES

Table A2.1 Variables of interest in NECSS subject database

Variable Name	Description	Coded Values
PERSON_I	Subject identifier	12 character alphanumeric
INTDATE	Date at interview	Date9.
PROV_ID	Reporting province	59 BC 48 Alb 47 Sask 46 Man 35 Ont 12 NS 11 PEI 10 Newf
SEX	Subject gender	M Male F Female
AGE	Age at interview	2 digit number
AGEGRP5	5-year age group	1 20-24 2 25-29 3 30-34 4 35-39 5 40-44 6 45-49 7 50-54 8 55-59 9 60-64 10 65-69 11 70-74 . >74
UNEMP	Never been employed	0 No 1 Yes
CONTROL	Case/control assignment	0 Case 1 Control
CA_SITE	Cancer site	NHL Non-Hodgkin's lymphoma CNTL Control
HISTOLOG	ICD-O morphology	10 character alphanumeric
ICD_CODE	ICD-O topography	13 character alphanumeric
EDUC_TOT	Total education	2 digit number
SCHOOL	Highest grade in secondary/elementary	2 digit number

Table A2.1 (con't) Variables of interest in NECSS subject database

Variable Name	Description	Coded Values
INCADQ	Income adequacy class	0 Low income 1 Lower middle income 2 Upper middle income 3 Higher income . Missing
INCOME	Total household gross income	N Prefer not to answer A < $10,000 B $10,000-19,999 C $20,000-29,999 D $30,000-49,999 E $50,000-99,999 F > $100,000 Missing
SMOK_CAT	Smoking status	1 Never smoked 2 Ex-smoker 3 Current smoker . Missing
SMOKED	Have smoked 100+ cigarettes	0 No 1 Yes . Missing
PACK_YRS	Pack-years of smoking	Number
BENZE_AH	Worked with benzene at home	0 No 1 Yes
BENZE_AW	Worked with benzene at work	0 No 1 Yes
HERBI_AH	Worked with herbicides at home	0 No 1 Yes
HERBI_AW	Worked with herbicides at work	0 No 1 Yes
PESTI_AH	Worked with pesticides at home	0 No 1 Yes
PESTI_AW	Worked with pesticides at work	0 No 1 Yes
RADIA_AW	Worked with radiation sources at work	0 No 1 Yes
WELDI_AH	Worked with welding at home	0 No 1 Yes

Table A2.2 Variables of interest in the NECSS occupational database

Variable Name	Description	Coded Values
PERSON_I	Subject identifier	12 character alphanumeric
TITLE	Job title	80 characters
JOB_TYPE	Type of industry and company name	80 characters
DUTIES	Main job duties	80 characters
YR_FROM	Job start year	4 digit number
YR_TO	Job end year	4 digit number
JOB_ID	Job history sequence #	2 digit number
FULL	Full time position	0 No 1 Yes
FULL_SE	Full time seasonal position	0 No 1 Yes
PART	Part time position	0 No 1 Yes
PART_SE	Part time seasonal position	0 No 1 Yes
OTHER_ST	Other than full/part time status	0 No 1 Yes

Table A2.3 Variables of interest in the NECSS residential database

Variable Name	Description	Coded Values
PERSON_I	Subject identifier	12 character alphanumeric
ELECTRIC	Home heating used electricity	0 No 1 Yes
UNKNOWN	Don't know primary type of home heating	0 No 1 Yes

Table A2.4 Derived variables in the NECSS subject database

Variable Name	Description	Coded Values
MATCHID	Pair identifier	
EDUCATION	Grade 12 education	0 No 1 Yes
SMK-PYRCAT	Pack-years of smoking categorized in four levels	0 None 1 1 to 9 pack-yrs 2 10 to 23 pack-yrs 3 Greater than 23 pack-yrs
BENZE_EX	Worked with benzene at home or work	0 No 1 Yes
HERBI_EX	Worked with herbicides at home or work	0 No 1 Yes
PESTI_EX	Worked with pesticides at home or work	0 No 1 Yes
PESTHERB_EX	Worked with pesticides or herbicides at home or work	0 No 1 Yes
WORKYRS	Number of full time equivalent years worked	Continuous
ELECTRIC_EV	Use of electric heat as a primary method of home heating ever	0 No 1 Yes
RADIATION_EV	Ever held a job with expert-assessed annual exposure to radiation exceeding 1 mSv	0 No 1 Yes
CUM	Cumulative exposure index with 2-year lag	Continuous
CUM_5YR	Cumulative exposure index with 5-year lag	Continuous
CUM_NOLAG	Cumulative exposure index with no lag period	Continuous
CUM_3TO12	Cumulative exposure index in 3-12 year exposure time window	Continuous
CUM_13TO22	Cumulative exposure index in 13-22 year exposure time window	Continuous
CUM_23TO32	Cumulative exposure index in 23-32 year exposure time window	Continuous
CUM_33TO42	Cumulative exposure index in 33-42 year exposure time window	Continuous
MAXMF	Highest MF exposure intensity in any job	0 Less than 0.3 μT 1 0.3 to less than 0.6 μT 2 0.6 μT or greater

Table A2.4 (con't) Derived variables in the NECSS subject database

Variable Name	Description	Coded Values
MFJOBLONGEST	MF exposure intensity in job held longest	0 Less than 0.3 μT 1 0.3 to less than 0.6 μT 2 0.6 μT or greater
YEARSEXP	Number of years worked in jobs with exposure above background level	Continuous
CUM4CAT	Cumulative exposure index with 2-year lag categorized in four levels	0 Zero 1 Above 0 to less than 6.0 2 6.0 to less than 20.0 3 20.0 or greater
CUM_5YRCAT	Cumulative exposure index with 5-year lag categorized in four levels	0 Zero 1 Above 0 to less than 6.0 2 6.0 to less than 20.0 3 20.0 or greater
CUM_NOLAGCAT	Cumulative exposure index with no lag period categorized in four levels	0 Zero 1 Above 0 to less than 6.0 2 6.0 to less than 20.0 3 20.0 or greater
CUM_3TO12CAT	Cumulative exposure index in 3-12 year exposure time window categorized in four levels	0 Zero 1 Above 0 to less than 5.0 2 5.0 to less than 10.0 3 10.0 to 20.0
CUM_13TO22CAT	Cumulative exposure index in 13-22 year exposure time window categorized in four levels	0 Zero 1 Above 0 to less than 5.0 2 5.0 to less than 10.0 3 10.0 to 20.0
CUM_23TO32CAT	Cumulative exposure index in 23-32 year exposure time window categorized in four levels	0 Zero 1 Above 0 to less than 5.0 2 5.0 to less than 10.0 3 10.0 to 20.0
CUM_33TO42CAT	Cumulative exposure index in 33-42 year exposure time window categorized in four levels	0 Zero 1 Above 0 to less than 5.0 2 5.0 to less than 10.0 3 10.0 to 20.0
YEARSEXPCAT	Number of years worked in jobs with exposure above background level categorized in four levels	0 Zero 1 0.25 to less than 5 years 2 5 to less than 17.5 years 3 17.5 to 50 years

Table A2.5 Derived variables in the NECSS occupational database

Variable Name	Description	Coded Values
MAGNETIC	Category of MF exposure in job	0 Insufficient information 1 Lesss than 0.3 μT 2 0.3 to less than 0.6 μT 3 0.6 μT or greater
MF	MF exposure intensity in job	0 Less than 0.3 μT 1 0.3 to less than 0.6 μT 2 0.6 μT or greater
RADIATION	Expert-assessed category of radiation exposure in job	0 Less than 1 mSv annually 1 1 mSv or greater annually
STATUS	Proportion of full time hours	Continuous between 0 to 1
YR_FROMIMP	Imputed job start year	4 digit number
YR_TOIMP	Imputed job end year	4 digit number

APPENDIX 3
DERIVATION OF EXPOSURE INDICES (Examples)

Two examples of the derivation of the magnetic field exposure indices are provided in this appendix. For the first example, consider a hypothetical subject with interview year 1996 who was 25 years old at interview and who had held three jobs: one a full time job from 1993 to 1996 with an original MF exposure assessment of greater than or equal to 0.6 μT, the second a part time job from 1991 to 1992 with a MF exposure assessment of less than 0.3 μT (category 1), and the third a full time seasonal job from 1988 to 1989 with a MF exposure assessment of between 0.3 and 0.6 μT (category 2). The portion of the exposure file that would be generated for this individual is shown in Table A3.1. It would contain seven observations; there would be no observation for year 6 as the subject did not hold a job that year and there would be no entry for year 8 as the subject was under 18 that year. The values for the MF intensity would be one less than the original values assigned for the exposure assessment categories. The exposure file would contain the data in the final six columns of the table. (The calendar year, subject age, and mathematical calculations are provided for ease of interpretation only.)

The cumulative exposure with a two-year lag index would start at year 3 (1993) and would be calculated as 2.0 + 0 + 0 + 0.5 = 2.5. The cumulative exposure with a five-year lag would be 0.5; the cumulative exposure in the 3-12 year exposure window would be 2.0 + 0 + 0 + 0.5 = 2.5; and the cumulative exposures in the 13-22, 23-32, and 33-42 year exposure windows would be 0. The duration of each job would be calculated as 1 year for job 1, 0.5 + 0.5 = 1 year for job 2; and 0.5 years for job 3. As there was tie for the longest duration between jobs 1 and 2, the exposure intensity

value of 2 for job 1 would be assigned as the value for the index EMF intensity in job held the longest as it is higher than that for job 2. The highest exposure in any job ever held would be 2, the maximum value in the MF intensity column from year 3 down. Finally, the number of work years would be calculated as 1.0 + 1.0 + 1.0 + 1.0 + 0.5 + 0.5 + 0.5 = 5.5 years; the values for years 0, 1, and 2 would be included in this sum.

Table A3.1 Created year-by-year exposure file for the first example*

Calendar year	Subject age	Person ID	Job Number	Year	MF exposure intensity**	Job Status***	MF cumulative exposure
1996	25	***3500***	***1***	***0***	***2***	***1.0***	2 X 1.0 =***2.0***
1995	24	***3500***	***1***	***1***	***2***	***1.0***	2 X 1.0 =***2.0***
1994	23	***3500***	***1***	***2***	***2***	***1.0***	2 X 1.0 =***2.0***
1993	22	***3500***	***1***	***3***	***2***	***1.0***	2 X 1.0 =***2.0***
1992	21	***3500***	***2***	***4***	***0***	***0.5***	0 X 0.5 = ***0***
1991	20	***3500***	***2***	***5***	***0***	***0.5***	0 X 0.5 = ***0***
1990	19	-	-	-	-	-	-
1989	18	***3500***	***3***	***7***	***1***	***0.5***	1 X 0.5 = ***0.5***
1988	17	-	-	-	-	-	-

* The bolded italicized entries would make up the file.
** The MF exposure intensity variable (values of 0,1,2) was re-scaled from the values assigned to the original MF exposure assessment categories (values of 1,2,3).
*** Job status was used to estimate the proportion of full time hours worked.

As a second example, consider a hypothetical subject with an interview year 1996 who was 25 years old at interview and who had held two jobs (where there was an overlap in the year between consecutive jobs): one a full time job from 1993 to 1996 with an original MF exposure assessment of greater than or equal to 0.6 μT (category 3), and the second a part time job from 1991 to 1993 with an original MF exposure assessment of between 0.3 and 0.6 μT (category 2). The portion of the year-by-year exposure file generated for this individual is demonstrated in Table A3.2. It would contain seven observations; there would be two observations for year 3. There would

Table A3.2 Created year-by-year exposure file for the second example*

Calendar year	Subject age	Person ID	Job number	Year	MF exposure intensity**	Job Status***	MF cumulative exposure
1996	25	***3600***	***1***	***0***	***2***	***1.0***	2 X 1.0 = ***2.0***
1995	24	***3600***	***1***	***1***	***2***	***1.0***	2 X 1.0 = ***2.0***
1994	23	***3600***	***1***	***2***	***2***	***1.0***	2 X 1.0 = ***2.0***
1993	22	***3600***	***1***	***3***	***2***	***1.0***	2 X 1.0 = ***2.0***
1993	22	***3600***	***2***	***3***	***1***	***0.5***	1 X 0.5 = ***0.5***
1992	21	***3600***	***2***	***4***	***1***	***0.5***	1 X 0.5 = ***0.5***
1991	20	***3600***	***2***	***5***	***1***	***0.5***	1 X 0.5 = ***0.5***
1990	19	-	-	-	-	-	-
1989	18	-	-	-	-	-	-

* The bolded italicized entries would make up the file.
** The MF intensity variable (values of 0,1,2) was re-scaled from the values assigned to the original MF exposure assessment categories (values of 1,2,3).
*** Job status was used to estimate the proportion of full time hours worked.

be no observations generated beyond year 5 as no jobs were held during that time period. The values for the MF intensity would be one less than the original values assigned for the exposure assessment categories. The exposure file would again contain the data in the final six columns of the table.

The cumulative exposure with a two-year lag index would be calculated as 0.5 (2.0 + 0.5) + 0.5 + 0.5 = 2.25; the two values for the MF cumulative exposure variable for year 3 would be averaged. The cumulative exposure with a five-year lag would be 0; in the 3-12 year exposure window 2.25; and in the 13-22, 23-32, and 33-42 year exposure windows 0. The duration of each job would be calculated as 0.5 X 1 = 0.5 years for job 1 and as 0.5 x 0.5 + 0.5 + 0.5 = 1.25 years for job 2; the duration assigned to each job for year 3 would be half the value of the status variable for that year. The exposure intensity in the job held the longest would thus be 1, the value of the exposure intensity variable for job 2. The highest exposure in any job ever held

would be 2, the maximum value in the exposure intensity column from year 3 down. Finally, the number of work years would be calculated as 1.0 + 1.0 + 1.0 + 0.5 (1.0) + (0.5) 0.5 + 0.5 + 0.5 = 4.75 years; the values for years 0, 1, and 2 would be included in this sum.