BIRTHWEIGHT, MATERNAL AGE AND SOCIAL CLASS AS RISK FACTORS FOR CHILDHOOD LEUKEMIA

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

The Faculty of Graduate Studies
The Faculty of Medicine
Department of Health Care and Epidemiology

We accept this thesis as conforming to the required standard:

THE UNIVERSITY OF BRITISH COLUMBIA

May 2000

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Date April 27, 2000

ABSTRACT

This thesis was designed to evaluate the effects of birth weight, maternal age and parental social class on the risk of childhood leukemia using a population based case control study of 798 participants in five Canadian provinces. Children between the ages of 0-14, who were diagnosed between 1990 and 1994 in Alberta, Saskatchewan and Manitoba, or 1990 to June 1995 in British Columbia and Quebec were eligible for inclusion in the study. Controls were matched on age, gender and province of residence. Response rate was 90% for cases and 76% for controls and data was collected via personal interview with parents. The primary area of investigation was the assessment of exposure to electromagnetic fields as a risk factor for childhood leukemia. Interview data on a large number of variables were available allowing for consideration of other potential risk factors. Univariate analysis suggested a case group with lower maternal age at birth, lower levels of household income, maternal and paternal education and occupational status. There was no evidence of a significant effect for birthweight on disease risk. In a multivariate analysis, four models were constructed encompassing variables related to social class, behaviour, demographics and environmental tobacco smoke. These were individually assessed using logistic regression techniques. The persisting variables were then combined and assessed in a final logistic model. Variables shown to affect disease risk in the final model were Asian ethnic origin, (OR = 3.65, CI = 1.27-10.52, p value = .02); maternal smoking of 10-20 cigarettes per day during pregnancy, (OR = 1.80, CI = 1.12-2.90, p value = .02); mother's usual occupation in high SES category, OR = 0.48, (CI = 0.26 – 0.88, p value = .02); maternal alcohol use of 1-2 drinks per week in the month before pregnancy, OR = (1.77, CI = 1.17 – 2.70, p value = .007).

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ACKNOWLEDGEMENTS

The principal investigators of the Childhood Leukemia Study, Mary McBride and Richard Gallagher, have been extremely generous in allowing me to base my project on their very compelling study. For that, I thank them. I also owe a debt of gratitude to my colleagues at the B.C. Cancer Agency: Sandy Malby for her conscientious attention to the details of data; Chris Bajdik for his concise clues to the mysteries of statistics.

The physical ability to produce a thesis is a gift not to be taken for granted. I owe profound thanks to Dr. Cecil Herschler, Dr. Andrew Feldmar and Herta Buller, R.M.T. for their diverse artistic, medical and scientific talents.

I am grateful to the members of my committee, Dr. Clyde Hertzman, Richard Gallagher, Dr. Susan Kennedy and Dr. John J. Spinelli for the depth of their knowledge and patience.

There are a number of friends I must acknowledge for the much appreciated and ever present back-up system they continue to provide: Katherine Kortikow, Kati Campbell and Anya Keefe. This manuscript was prepared with inordinate capability by Heather Neidig.

Above all, my thanks must go to the 798 families across Canada who voluntarily gave of themselves and their time...half of them in the midst of intense personal crisis and the other half wishing to be of assistance.

DEDICATION

This thesis is dedicated

in every respect

to

Evan

CHAPTER 1: INTRODUCTION

1.1 Research Question

Do birthweight, maternal age and parental social class have an effect on risk for childhood leukemia?

1.2 Rationale

Childhood cancers account for just 2% of the cancer burden in developed countries (Little 1999) but are of immense public health importance. While not accounting for a large proportion of cancer cases, cancer is the second commonest cause of death, after accidents, for children up to age 14 in Canada (Canadian Cancer Statistics 1999) and other developed countries (Little 1999). The total potential years of life lost in Canada due to cancer deaths in children aged 0-14 in 1996 was 13,514 years (Canadian Cancer Statistics 1999). It is estimated that more than 100,000 person-years of life are lost to childhood cancer in the U.S. each year (Ross *et al.* 1993).

Childhood leukemia is the most common type of pediatric cancer accounting for about 33% of all cancers in children. It is a rare disease, with an incidence rate in Canada of approximately 48 new cases per million per year in children under 15 years old (Canadian Cancer Statistics 1999).

Due to significant progress in therapy, mortality rates have been significantly reduced however there are long-term health implications for survivors. In addition, there is often severe associated psychological, emotional and financial impact on the child, family, relatives and friends (Little 1999).

The etiologic factors involved in the development of childhood leukemia remain unknown. Some rare genetic conditions have been linked with childhood leukemia and an association with ionizing radiation in utero is well established however these exposures are uncommon and cannot completely account for the incidence rates of this disease.

The data set for this study was drawn from the largest case control study of childhood leukemia ever undertaken in Canada, presenting a unique opportunity to estimate the effects of birthweight, maternal age and parental social class on leukemia risk. While these factors have assumed some importance in the literature, small numbers or inadequate design and procedures have hampered previous studies. This study features a combination of high numbers of participants in a prospective design that includes extensive data on each subject. In addition, no previous Canadian study has examined these factors.

CHAPTER 2: LITERATURE REVIEW

2.1 Descriptive Epidemiology of Childhood Leukemia

Between 1990 and 1994, approximately 879 new cases of childhood cancer were diagnosed yearly in Canada, resulting in an overall rate of 150 new cases per million children per year. (Canadian Cancer Statistics 1999).

Among the childhood cancers, the acute leukemias are the most common, accounting for about 31 % of all newly diagnosed cases. (Canadian Cancer Statistics 1996). Childhood leukemia is a heterogeneous group of diseases. Acute lymphoblastic leukemia (ALL) is the most common form, accounting for 80% of leukemias. Acute myelogenous leukemia (AML) or acute nonlymphoblastic leukemias (ANLL) is the next most common form at 17% of all cases. Chronic myelogenous leukemia (CML) and juvenile chronic myelogenous leukemia (JCML) contribute the remainder (Neglia and Robison, 1988). All of these leukemia types can be further subcategorized by morphologic and immunophenotyping classifications schemes which may be of potential epidemiologic importance. It is plausible that specific risk factors may be associated with specific subclasses.

ALL has an age-related incidence that characteristically peaks between the ages of 1 and 4 years (Little 1999). The importance of this early peak is not understood, however, it may point to causes that operate during the prenatal or perinatal period. During the prenatal period, differentiation of primitive cells is occurring and the initial development of the immune system is taking place. These are critical circumstances in which the fetus is potentially sensitive to external influences. Gestational factors have also been speculated upon as events of etiologic importance that may be markers of either a common environmental exposure, an abnormal intra-uterine environment or a genetic predisposition.

ANLL does not demonstrate the same peak incidence during the early years of life (Neglia and Robison 1988). Etiologic factors for ANLL are generally not known and the low incidence of this subtype makes it difficult to study. Investigation of environmental factors, particularly industrial chemical and pesticides, are still in the hypothesis-generating stage, extrapolated from findings for adult leukemias.

2.1.1 Time Trends

Childhood leukemia, more than any other childhood cancer, has had extensive investigation for time trends. Unfortunately, findings are often difficult to interpret and no overall consistency has been established (Draper *et al.*, 1994). Studies tend to cover a variety of time periods and use different analytic methods. Study results resist comparison because studies analyze and report results utilizing different age, gender and subtype groupings.

One of the major issues is whether a reported moderate increase in ALL in industrialized nations beginning in the mid 70's is an artefact of diagnostic shifts and more accurate classification. Although it is agreed that some part of the rise in ALL is due to changes in diagnosis and classification, it is not clear how much of the increase can be explained by these factors.

The Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute in the U. S. gathers data on childhood cancer incidence and patterns from five states (Connecticut, Utah, New Mexico, Iowa and Hawaii) and five metropolitan areas (Detroit, Atlanta, Seattle, San Francisco and Los Angeles) comprising about 14% of the U. S. population.

Miller (1992) demonstrated that the increased incidence for ALL between 1973 and 1987 reported for the populations that fall under the SEER registries in the U.S. was mainly accounted for by changes in diagnosis which altered the incidence of specific leukemia subtypes.

In a recent publication covering the period from 1977 to 1995, (Ries *et al.*, 1999) the SEER Program reported an estimated annual percentage change of 0.9% for total leukemia. This increase was driven by an increase in ALL during this period. Although the rates of other leukemias did not rise significantly from 1977 to 1995, small numbers for the rarer subtypes results in considerable scatter in yearly rates rendering interpretation of trends rather difficult.

A closer inspection of this SEER model of a constant moderate yearly increase in the ALL rate reveals a complex picture. For instance, there is a different time trend pattern for the Los Angeles area compared with the other 9 areas. The other areas have had more or less stable rates since 1984. The Los Angeles area has shown more variability with high rates in the late 70's, then decreasing in 1984-85 and subsequently rising to rates above the other areas. When rates are calculated separately for Hispanic and non-Hispanic children it is apparent that rates for non-Hispanic children are similar to children in other areas, but rates for Hispanic children are much higher (Ries *et al.*, 1999). Los Angeles experienced a dramatic change in population composition from 1990-1995 when the population of Hispanic children under 15 increased and the population of non-Hispanic children greatly decreased. It is believed that the increase in ALL rates for the whole SEER population are at least partially explained by the increased percentage of Hispanic children in Los Angeles.

Parkin *et al.* (1996) looked at data from 36 cancer registries in 23 European countries to evaluate temporal trends for all leukemias together post Chernobyl. The age-standardized incidence rate rose modestly by 0.6% a year from 1980-86 and 0.4% per year from 1987-91. The rise was most evident for children aged 1-4 years.

At this point in time, there is no definitive explanation for the generalized small increased incidence of ALL, although changes in diagnosis and classification, immigration shifts between populations with large differences in incidence rates into areas covered by registries and environmental exposures are all being considered as possible factors.

2.1.2 Mortality and Survival

The overall survival rate for children with leukemia has improved greatly over time, principally due to refinements in treatment regimens, however the chance of survival varies greatly with subtype.

Canadian Cancer Statistics (1999) reports an age-standardized five year survival rate of 80 % for all leukemias; 89% for ALL and 60% for non-ALL leukemias. These figures are encouraging, but represent an unmeasured overestimate of survival since deaths occurring after the age of 14 years are not included in the calculations. Also, survival is highly correlated with age at diagnosis.

The SEER program recently reported 5-year survival rates for childhood leukemia for their jurisdiction. Survival rates for ALL increased from 61% to 77% from 1975-84 to 1985-94. The most favourable prognoses were in the 1- 4 year age group with a 5-year survival of 85%. Those aged 5-9 had an 80% survival rate; infants had the poorest outcome with a 37%

survival rate. The higher survival rate for children aged 1-9 is likely related to the higher proportion of low risk ALL cytogenetic subtyping found in this age group (Ries *et al.*, 1999).

ALL survival rates were slightly higher for females than for males and for white children over black children in the U.S. It was thought that the poorer outcome for black children may represent individual variation in pharmacodynamics of treatment drugs however black children also tend to have an excess of the least curable cytogenetic subtypes of ALL.

While there has also been improvement in survival rates for children with AML, the rate was markedly lower than ALL. The 5 year survival rate in the U. S. was only 41% for the period 1985-94. In contrast to ALL, all age groups have a similar outcome with the younger than 5 year age group having a slightly poorer outcome than the older groups. The outcome for females is slightly better than for males and whites and blacks have similar survival rates (Ries *et al.* 1999).

2.1.3 Geographical Variation/Incidence, Canada and International

Based on data collected from registries around the world between 1970-79, rates for all childhood leukemias combined ranged from 15 to 56 per million. (Linet 1991). Parkin *et al.* (1998) reported Costa Rica as having the highest annual rate at 59.4 per million while the lowest, 11.8 per million was observed in Ibadan, Nigeria. International incidence figures show a much higher incidence of childhood leukemia in white populations of industrialized countries compared to Third World countries or black populations within North America. In the white populations of North American and in Australia, Japan, Singapore, the Philippines, north and western Europe and non-aboriginal New Zealand, the incidence was between 35

and 49 per million (Parkin *et al.*, 1998). The incidence rate for Canada for 1990 – 1994 was 47 per million (Canadian Cancer Statistics 1999). Within the U.S., Hispanic males in Los Angeles have one of the highest rates at 63.6 per million, while U.S. blacks have among the lowest rates at between 25-28 per million. An incidence of less than 25 per million prevails in India, Africa and among native Kuwaitis (Parkin *et al,* 1998).

As the most common form of childhood leukemia, it is valuable to look at incidence data for ALL separately. The geographical distribution of ALL features higher rates in white North American and European populations than in Asian populations and substantial variation in incidence across continents and within populations. The incidence rate for Canada for 1990 – 1994 was 38 per million. (Canadian Cancer Statistics 1999) Costa Ricans and Hispanics from Los Angeles again have the highest incidences at 44.7 and 48 per million respectively. Areas of Brazil, India and Kuwait have values below 12 per million (Parkin et al, 1998 or 88).

In Europe there is a two-fold difference in incidence ranging from 17.8 in Slovenia to 36.4 in West Germany. The rates for whites in the U.S. are about twice that for blacks and in Israel, the incidence is 50% higher for Jews than non-Jews. (Parkin *et al.*, 1998).

It is of interest to note that the peak in incidence of ALL is by no means consistent across geography or temporality. It is conspicuously absent in Africa and many developing nations. It evolved in Britain and North America in the 1920's and 30's pointing to some association with industrialization. As well, the peak was observed earlier in American whites than blacks, and whites currently have a 20-30% higher incidence possibly signifying socioeconomic factors although the possibility of underascertainment in disadvantaged populations must also be taken into consideration.

As well as variations in incidence, the rank of cancer as a cause of death varies geographically with lower rates in the Third World. During the period 1982-1984, cancer was the 9th cause of death in boys and the 10th in girls under 15 in Bombay, India. (Krishnamurthy 1991). Data from Africa is limited to small areas and is unreliable, but shows that cancer ranks higher among the causes of death for children than it does in India. This is thought to be due to higher rates for Burkitt's lymphoma and HIV infection. (Parkin *et al.*, 1988). These rates in the Third World are likely affected by competing causes of mortality and it is probable that as communicable disease is brought under control in these regions, cancer rates will rise.

The global and regional patterns indicating that the incidence of leukemia subtype is not geographically uniform suggests at least two avenues of investigation for etiologic clues. Unidentified racial/genetic factors particular to ethnic groups or families may account for some of the variation. These genetic factors may be inherited or mutations as a consequence of exposure to environmental mutagens. As well, differentiation in incidence may be the result of environmental influences specific to a region. This might include exposure to a wide range of toxins; infectious agents; lifestyle factors of cultural groupings or socioeconomic factors.

In summary, it is difficult to accurately interpret global incidence and mortality data for childhood leukemia. The problem is particularly acute with data from developing countries. Where they exist, many registries are not population-based but collect data from hospital admissions. There are problems with lack of referral to these hospitals for treatment due to poverty; difficulties of travel to a specialized centre; lack of resources to perform histopathological assessments; poor diagnostic information or preference for traditional

medicine. As well, lack of stability of the population can lead to difficulty in defining the denominator for calculation of incidence rates (Little 1999).

2.1.4 Current Etiologic Hypotheses

The current state of knowledge supplies very few clues as to the etiology of childhood leukemia. With the exception of prenatal exposure to x-rays and specific genetic syndromes, there is a dearth of information on risk factors and their mode of action during the prenatal and neonatal period. The pattern of tumors in childhood is different from adult cancers, suggesting different etiologic factors. Childhood cancers differ in site, histology and clinical behaviour. Childhood cancers tend to have short latent periods, often grow rapidly and are aggressively invasive. These cancers generally are more responsive to chemotherapy than adult cancers because rapidly growing cancers show better cell kill by chemotherapy and radiation.

The genetic environment offers a fertile area in the search for potential risk factors given that some genetic conditions are already strongly associated with childhood leukemia. There is the possibility of inherited genetic susceptibility due to spontaneous mutation or environmental exposure causing germ cell mutation. The mechanisms differ for mutation arising in maternal and paternal gametes. Genetic point mutations occur more commonly in male gametes in preconception. In the mother's case, new oocytes are not formed after birth, so a germ cell mutation arising in the index child may be attributable to exposures in the maternal grandmother of the index child before the birth of the mother of the index child.

Apart from inherited mutagenic effects, an environmental agent may cause cancer in at least four ways. Firstly, the index child may be exposed to an agent in his or her own

lifetime directly or indirectly through breastfeeding. Secondly, the mother may be exposed to an agent during pregnancy, thus exposing the child directly. Thirdly, a future mother may be exposed to an agent with slow metabolic clearance resulting in an embryotoxic dose in early pregnancy. Fourthly, toxic exposure may cause reproductive system damage before pregnancy, which compromises the development of the fetus.

The study of childhood cancer provides a unique opportunity to investigate the impact of environmental factors. The period of latency is usually much shorter than adult cancers and exposures under investigation would most likely be unconfounded by occupational exposures and smoking or alcohol use.

A number of specific hypotheses are currently being investigated worldwide. The apparent tendency of childhood cancer to cluster has made it a prime candidate as a virus-related condition. The so called "viral hypothesis" has to do with a delayed pattern of infections that allows ALL to occasionally develop, possibly through alteration of immune function (Greaves 1997). Attention has been directed to the infectious disease patterns within "isolated" and "non-isolated" communities displaying variation in leukemia incidence. (Kinlen and Petridou 1995).

As well, there has been extensive investigation of exposure to electro-magnetic fields beginning with a report from Wertheimer and Leeper (1979). This study found a two to three fold excess of cancer mortality among children living in Denver, Colorado in homes with presumed higher magnetic fields as indicated by local power line configurations. Subsequent studies have been greatly refined and have utilized more precise metrics, but have reported conflicting results. The main study from which data for this thesis was drawn, recently published a report (McBride *et al.* 1999) which concluded there was little support for a

relationship between power-frequency electro-magnetic fields and risk of childhood leukemia.

2.1.5 Limitations of Data

The potential for insight into etiology of cancer is the prime motivation for exploring descriptive epidemiological features of the disease. However, this is not as straightforward a procedure with childhood cancer as it is for adult cancers. Until recently, many registries were coding childhood cancers by anatomical site. Site-based classification systems are not adequate for collecting data on children since childhood tumours are histologically diverse and can occur at several sites. Also data was collected at some registers whose population base was too small for reliable calculation of incidence rates. As well, there are concerns about variation in the completeness of registration, problems with miscoding and misclassification (Parkin *et al.*, 1988). It is only relatively recently that data of high quality has been collected from many parts of the world.

2.2 Risk Factors

2.2.1 Maternal Age

A number of epidemiological studies have reported negative results with respect to advanced maternal age.

Graham (1966) carried out a case control study of 319 children with leukemia in the New York, Baltimore and Minneapolis areas using parent interviews. No difference was found in ages of mothers at birth. Data on potential confounders included exposure to ionizing radiation in parents and children and previous miscarriage. Shaw (1984) found no

association with maternal age in a California case control study of 255 leukemia cases diagnosed between 1975 and 1980 using birth certificate data. Additional data derived from birth certificates included birth order and paternal occupation from which socioeconomic status and benzene exposure was inferred. No other data on potential confounders was available.

Van Steensel-Moll (1985) conducted a case control study on 519 ALL cases diagnosed in the Netherlands between 1973 and 1980. Data was collected via mailed questionnaires and no association was detected between maternal age and ALL risk. Data was collected on a wide range of potential confounders including exposure to ionizing radiation, viral infections, oral contraceptives, smoking and alcohol use. No association with increasing maternal age was found by Shu (1988) in a case control study involving 309 leukemia cases carried out in Shanghai. As well, a nation-wide nested case control study in Sweden (Cnattingius *et al.*, 1995) utilizing a cohort of all live births since 1973, identified 613 cases of ALL in birth cohorts from 1973 to 1989. Five controls were matched to each case. The authors reported finding no association with maternal age.

A recently published study by Smulevich (1999) reported findings from a case control study of cancer risk factors for children in Moscow on a total of 593 cases diagnosed from 1986 – 1988. The study looked at ages of both parents at the birth of the index child. No association was found with maternal age. Paternal age showed a non-significant effect with a slight positive trend for increasing age. The authors postulate that the effect of father's age on cancer risk may be stronger than that of the mother due to the possibility of gene mutation in male germ cells.

Several reports have documented an increased risk of childhood leukemia in children born to older mothers. These are mainly earlier studies based on mortality data.

One of the earliest studies reporting positive findings was a large case control study of childhood leukemia in England and Wales (Stewart 1958). Mothers of children who had died of leukemia or cancer between 1953 and 1955 were traced in order to conduct a personal interview. Controls were the mothers of children without cancer matched for age, gender and locality. The authors reported a total of 1,694 deaths of which 792 were ascribed to leukemia and 902 to other cancers. Interviews were completed for 85% of the leukemia cases and 82% of the cancer cases. This study collected data on a wide variety of potential confounders including ionizing radiation exposure of mother and child, maternal smoking, congenital defects and diet of the child. The study found that the risk of dying of leukemia before the age of 10 was twice as great, if the mother was over 40 years old at the birth of the child.

Stark and Mantel (1966), in a study examining both "mongolism" and leukemia risk, investigated 706 leukemia deaths among children born 1950 – 1964 in Michigan using death records for ascertainment. The data showed that risk of death from childhood leukemia increased with advancing maternal age. No mention is made of excluding children with Down's Syndrome from the analysis for leukemia risk.

An early study in California (Fasal *et al.*, 1971) derived data from birth and death certificates on 802 children who died between ages 1-9 of childhood leukemia from 1959 to 1965. Fasal found a non-significant increase in risk with advanced maternal age. The risk increased across age categories, except in the highest age group of mothers older than forty years, where it dropped below the level for the youngest age group. Kaye *et al.* (1991) used a case control design and birth registration data on 337 cases diagnosed in Minnesota between

1969 and 1988 to study various birth characteristics in relation to ALL risk. The analysis demonstrated a significant positive association in relation to advanced maternal age finding a twofold increased risk of ALL for births to women older than 35 years. An analysis of data obtained from interviews with parents of ALL cases and a set of community controls investigated maternal age as a risk factor across four immunopathological subtypes (Buckley 1994). The study was conducted in 25 institutions across the U.S. with 1282 ALL cases. Maternal age greater that 35 years was confirmed as a risk factor for 3 of the 4 subtypes (OR = 3.4, p = .001 for T-cell ALL). However, only 50% of eligible cases participated in this investigation.

Overall, the inconsistency of the data on maternal age is difficult to interpret. Potential mechanisms to support risk at advanced age would include chromosome breaks and toxic insult to older eggs. The usually higher level of socioeconomic status at advanced age may explain findings that show no effect or a protective effect for older mothers.

Risk estimates from earlier studies which relied on death records did not account for Down's Syndrome, a genetic disorder known to be specifically associated with childhood leukemia as well as advanced maternal age. The relative risk of childhood leukemia associated with Down's Syndrome is extremely high, around 30-fold (Little 1999).

In addition, many of these studies were conducted during the period of the 60's to the 90's. During this time period, social change affecting reproduction such as widely-available, effective contraception and abortion services began to influence maternal age at birth. Little (1999) has put forward for consideration the question as to whether inconsistency in the findings regarding maternal age reflects sociological rather than biological influences.

2.2.2 Birth Weight

A number of studies using a variety of methods have investigated the association between birthweight and risk of childhood leukemia.

The California study by Fasal *et al.* (1971) found that birth weight greater than 8.5 lbs. was significantly associated with leukemia mortality for females only, with an odds ratio of 2.1. Maternal age, birth order and social class were also investigated, but data on other potential confounders was not available. Wertelecki and Mantel (1973) compared birthweight ranks among 72 ALL cases and their siblings demonstrating an association between elevated birthweight and ALL. Children who developed ALL had significantly greater birthweights that expected in all comparisons.

Daling *et al.* (1984) reported an association between heavy birthweight and leukemia risk in U.S. children younger that two years old. Hirayama (1980) showed that leukemia risk for Japanese children before age two was 69% higher in those weighing 4 kg or more at birth than those weighing 3.4 kg or less. Robison *et al.* (1987) demonstrated two-fold risks for children with birthweights over 4000 gm.

The first analytic study of childhood leukemia ever conducted in China (Shu *et al.* 1988) used a case control interview design to investigate a wide variety of various risk factors in 309 cases in Shanghai. The authors reported an association between birth weight greater than 3500 gm. and leukemia risk in children under 6 years old (OR = 1.7, p =.01).

In a study published in 1991, Kaye *et al.* found no overall association between birthweight and ALL. However, children with an elevated birthweight of more than 3,800 gm. who were diagnosed before the age of 4 demonstrated a significant increase in risk. Savitz *et al.* (1994) showed no association between elevated birthweight of more than 4000

gm. and risk of ALL. This case control interview study was carried out in Denver, Colorado retrospectively ascertaining cases that had been diagnosed between 1976 and 1983. Controls were ascertained using different eligibility criteria from cases resulting in potential selection bias. The case group was drawn from "all other cancers" and the study was not able to examine previously reported increased risk in ALL cases diagnosed at an early age due to inadequate numbers. Poor subject response rate was also a concern on this study; 68% for cases and 60% for controls.

In Buckley's (1994) case control study, an analysis stratified by immunophenotype demonstrated that cases with ALL in all subgroups tended to be heavier at birth than their controls. Cnattingius *et al.* (1995) reported a significant increased risk with birthweight of more than 4500 gm. and incidence of ALL in children diagnosed prior to age 2 or after age 5 (OR = 3.2 and 2.5 respectively). The investigators attempted to elucidate some of the underlying causes associated with high birthweight, however maternal age, multiparity, prolonged gestation and maternal diabetes did not account for the association between high birthweight and ALL.

The case control study by Smulevich *et al.* (1999) of cancer risk factors for children in Moscow analyzed data on a total of 593 cases. Based on 199 cases who were identified as having a diagnosis of leukemia, the authors reported an significantly elevated risk for children of full term pregnancies weighing 2,500 gm. or less at birth (OR = 4.7,CI = 1.4 – 16.5).

There are numerous risk factors for both high and low birth weight, many of which are interrelated, such as maternal age, maternal health status and maternal nutrition. It is worth noting that studies considering the association between birthweight and childhood

cancers are carried out almost exclusively in developed countries. In looking at the etiology of low birthweight in industrialized countries, the most important single factor is maternal cigarette smoking, followed by poor gestational nutrition and low pre-pregnancy weight (Kramer 1987). The reason for a possible association between high birthweight and leukemia is not understood. Doll (1989) suggested that a possible explanation for boys being at higher risk for leukemia than girls may be that the slightly higher birthweight of boys resulted in a relatively larger number of dividing cells in the tissue from which leukemia arises. In any case, it is evident that how these underlying attributes may affect risk is not at all clear.

2.2.3 Social Class

Socioeconomic status may serve as a marker for a number of environmental exposures and genetic factors such as race, maternal age and occupation. Gradients in the occurrence of disease by socioeconomic status can be a starting point for the formulation of more specific hypotheses. However, socioeconomic status has been relatively little studied in relation to childhood leukemia.

Some studies of social class and childhood leukemia have indicated that it is a disease of middle and upper middle class children. The reported association is weak and many of these studies have inadequacies including ascertainment problems. Also many studies have based data on categorized socioeconomic status according to community indicators derived from census or area data rather that according to individuals being studied

Sacks and Seaman (1947) showed a rising mortality rate for both adult and childhood leukemia paralleling a rise in economic status in Baltimore for 1939 to 1943. Walter and

Gilliam (1956) found that the leukemia mortality rate in the U.S. was higher for white than non-white children between 1950 and 1959.

In the same study that investigated birth weight and maternal age, Fasal *et al.* (1971) reported that social class showed significant positive association with leukemia mortality. Risk was demonstrated to be greater for children of higher social class, with significance confined to female cases. Relative risks were 1.7 for females and 1.1 for males. Fasal determined social class from occupation of the father at time of child's birth, but noted that these occupations tended to change between birth and diagnosis date.

Above-average social class, as determined by fathers occupation at time of diagnosis was found to be associated with incidence of ALL in and Australian study by McWhirter (1982). A proportional mortality analysis (Sanders *et al.* 1981) relating deaths among children in England and Wales to occupation of father at time of death showed an association between higher social class and death from leukemia with PMR's of 141 and 123 reported for time periods 1959-63 and 1970-72. Daye *et al.* associated a significantly increased risk of ALL with births to mothers with a high school or greater education (OR = 1.61, p = .03).

Geographic correlation techniques have also been used to study the relation between social class and childhood leukemia incidence. Pinkel and Fnetzger (1959) studied residence by census area in Buffalo, N.Y. and found the incidence of leukemia to be significantly higher in the upper economic half. A study by census area in Denver, Colorado by Githen (1965) demonstrated that the incidence of leukemia was two to almost four times higher in children living in census areas of high socioeconomic status compared with children living in the areas of lowest socioeconomic status. A study of leukemia incidence in 22 counties in England and Wales showed a significant relative risk of 1.49 for childhood leukemia in

electoral wards with the highest category of socioeconomic status. A gradient of risk was observed over the four categories of electoral ward. (Alexander *et al.*,1990)

Shu (1988) reported that parents of Shanghai leukemia cases tended to be better educated although this finding did not attain significance. Control selection bias may have played a role in minimizing this finding given that cases were ascertained retrospectively over a twelve-year period, while controls were ascertained prospectively. Adjustments were made for exposure risk variables by truncating the number of years of exposure for controls to be similar for that of cases, but this could not take into account calendar time differences. Therefore, controls were ascertained in a time period when educational opportunities were more available than in the time period when the cases were diagnosed.

A number of studies have found no association with social class. The early case control study by Stewart (1958) which conducted personal interviews with the mothers of 677 leukemia cases in England and Wales found no association with socioeconomic status as determined by occupation of the father and family income. A U.S. case control study by Graham (1960) also found no association between father's occupation and education and risk of childhood leukemia, however the case group did contain significantly more white that non-white children.

Shaw (1984) found no socioeconomic differences in a California case control study of childhood leukemia using paternal occupation on birth certificate as an indicator. Graham *et al.* (1960) in a study of all cancers found no correlation between social class by area of residence in Buffalo and childhood leukemia. However, he concluded the small number of leukemias available for analysis was probably not sufficient to permit detection of any effect.

In a recent case control study, Smulevich *et al.* (1999) looked at socioeconomic status in relation to childhood cancer in Moscow. Occupation and educational level were determined for both parents, however, methodology for classifying educational level was not reported in detail. Occupation was dichotomized as blue collar and white collar. No association was found between cancer risk and socioeconomic status in this study. The authors speculate that at the time of the study, differences in educational level did not translate into differences in income level or living conditions. As well, blue-collar incomes were often higher than the white-collar incomes of teachers, physicians and managers. Access to medical care was generally regarded to be the same among all segments of the population. Adjustment for lifestyle factors such as smoking and alcohol intake did not affect estimates for socioeconomic status.

Difficulties in assessing the findings of studies examining social class stem from the difficulty in measurement and interpretation of key indicators. For instance, socioeconomic indicators based on occupational classification may not capture disparities in working and living conditions across gender and racial or ethnic origin. As well, occupation-based measures have no application for social groups outside the labour force. This means the unemployed, homemakers, children, students, the retired and workers in illegal market sectors cannot be accounted for.

Education is another commonly used metric for socioeconomic status. It cannot be assumed that effects associated with a given level of education will be consistent for all groups. Economic returns for a certain level of education may vary within occupational groups, ethnic and racial groups and most certainly by gender. The social meaning of a specific level of education also varies across birth cohorts. For instance a high-school

diploma earned in 1940 has different social value and income potential from a diploma earned in 2000 and therefore may imply different exposures.

There are limitations with the use of neighbourhood data as an estimate of individual social class. The composition of neighbourhood can change over time and census data may be outdated depending on timing of analysis. As well, the advantages of such an analysis may be compromised when the metrics of an area are attributed to an individual.

Finally, there is an emerging area of investigation for population health research which has not yet been applied to childhood cancer. The connection between low socioeconomic factors and stress as a risk factor for childhood leukemia has not been studied. However, the recognition that components of stress response can alter the immune system provides an important key for thinking about the way immune function interfaces with behavioural response and potentially affects disease risk. Lovallo (1997) traces the sequence of biological events that begins when stress signals structural defence mechanisms to alter activity in important limbic structures which in turn signal the hypothalamus to modify both hormonal secretions via the adrenal gland and sympathetic outflow by the autonomic nervous system. The adrenal and sympathetic components of the stress response have pervasive influence on the immune system. Changes in autonomic activity affect lymph tissues and alter the development and activity of populations of lymphocytes including natural killer, T and B cells. The release of hormones, particularly cortisol, inhibit immune function by reducing the frequency and strength of immune function messages and reducing the numbers and activities of cells carrying out the immune response. In brief, it has been demonstrated physiologically that the immune status of an individual can change as a function of stress. Evans *et al.* (1994) discusses the same biological pathways in relation to the stress-mediated

reactions to socioeconomic disadvantage and posits that "socioeconomic disadvantage or other forms of stress do, indeed, appear to lead to adverse health states".

2.2.4 Parental Smoking

A thorough assessment of the role of cigarette smoking in the etiology of childhood cancer has yet to be completed. The potential sources of exposure for a child at all stages of development are varied, especially if parents are active smokers. Prior to conception, there is the possibility of genetic mutation to maternal or paternal germ cells.

Prenatally, there may be direct exposure through active maternal smoking or via maternal exposure to environmental tobacco smoke (ETS). Postnatally a child may be exposed via direct exposure through breast milk or through ETS.

With increasing restriction on smoking in public places in Canada, the home is quickly becoming the last bastion of an unregulated smoking environment. This has special implications for the involuntary exposure of infants and children. For them, the most single important point of exposure is the home.

ETS is a complex mixture of chemicals generated during the burning of tobacco, including irritants and systemic and reproductive toxicants, mutagens and carcinogens such as benzo(a)pyrene and formaldehyde. Over 50 compounds in tobacco smoke have been identified as carcinogens (IARC 1986).

Smoking is an established cause of a number of cancers. Among the health effects causally related to ETS are a number of developmental, respiratory, carcinogenic and cardiovascular effects. There are, in addition, effects for which evidence is suggestive of an

association but confirmation is not yet final. Other endpoints, including some rare childhood cancers, have not yet accumulated a weight of evidence in either direction.

There is increasing evidence that cigarette smoking may be causally related to leukemia in adults. (Austin and Cole, 1986; Brownson *et al.* 1993) Cigarettes contain compounds associated with increased risk of leukemia in adults such as benzene, nitrosamines, urethane and radioactive compounds. Relative to body weight, similar doses may have an amplified effect in children. It has also been confirmed that the home is the greatest source of ETS exposure for children.

A number of different exposure measurement techniques and study designs for determining exposure to cigarette smoking and environmental tobacco smoke (ETS) and their correlation with childhood cancer and leukemia have been reported in the literature over the past two decades.

Exposure Characterization Studies

A California study conducted statewide (Jenkins *et al.* 1992) used telephone interviews of 1,579 adults who reported exposure to ETS along with average daily duration for their household. Results for children showed that about 45% of infants and preschoolers and 38% of those under age 12 were exposed to ETS at some point on a typical day. The average duration of exposure for infants/preschoolers and adults was identical, about 4 hours.

Lum (1994) studied relative contribution of different daily environments to overall ETS exposure. For children age 0-5, 62% of ETS exposure occurs in the home, for those aged 6-11, 54% of exposure occurs at home and for adolescents, 41% occurs at home. Chilmonczyk *et al.* (1990) reported on a large population-based study of 518 infants, 6-8

weeks old, receiving routine wellness care in Portland, Maine. Results showed that 80% of the infants had detectable concentrations of urinary cotinine and 41% of infants lived in a household with one or more smokers. The results suggest that infants in non-smoking homes had other sources of exposure to ETS.

In a study for the National Center for Health Statistics in the U.S., Overpeck and Moss (1991) collected ETS data for 5,356 children up to the age of five. This was a cross sectional survey with the sampled group representing 86% of American children in the 0-5 age group. The study found that almost 50% of American children are exposed to ETS via prenatal maternal smoking and/or postnatal smoking by household members. Of the total sample, 1.2% were exposed prenatally only; 21% were exposed postnatally only; 28% had both pre- and postnatal exposure. The survey also found that 58% of children from the lowest income families lived with a current smoker in contrast to 30% of children from the highest income level. Mother's level of education was also associated with smoking, with 61% of children whose mother had not completed high school being exposed to household smoking versus 28% of children whose mothers had completed one year or more of college.

Biomarker Studies

Biomarkers are often used to study exposure prevalence. Most often this is done by direct analysis of physiological fluids for tobacco smoke constituents or their metabolites. Nicotine, cotinine and specific DNA adducts are the most widely used biomarkers of ETS exposure.

Although nicotine and cotinine are not directly related to a carcinogenic effect, they are measured because they are specific to tobacco smoke and their presence can generally be attributed to exposure to tobacco smoke.

The relationship between a biomarker and exposure is not straightforward due to disparity in biological and environmental microclimates being measured. Some of the difficulties associated with biomarker studies have to do with the variation in individual exposure due to biological factors such as uptake, distribution, metabolism and excretion in the human body. The physical microenvironment within which the exposure takes place necessarily involves spatial and temporal fluctuation induced by such factors as rate of smoking, ventilation, air mixing, room size etc. As well, individuals move among a multiplicity of microenvironments on a daily basis. A large body of literature has demonstrated that the levels of ETS encountered by infants and children pre- and postnatally are sufficiently high that ETS constituents are detectable in body tissue and fluids.

In Chilmonczyk's (1990) study of infants in Maine, information on household smoking habits was collected and urinary cotinine assays were carried out on all 518 infants. A concentration of 10 ng/ml was defined at the cutpoint for significant ETS exposure. Median urinary cotinine results were as follows: 1.6 ng/ml in the 305 non-smoking households; 8.9 ng/ml in 96 households where mother did not smoke but others did; 28 ng/ml in 43 households where only the mother smoked; and 43 ng/ml in the 74 households where both the mother and another household member smoked. In addition, in households where the mother smoked and breastfed, significantly higher levels of urinary cotinine were present in infants. In the absence of another smoker in the house, the level with breastfeeding and

maternal smoking was 87ng/ml. With another smoker present the median cotinine level for breastfed infants was 213ng/ml.

A number of other studies have attempted to distinguish exposure due to ingestion of mother's milk as opposed to inhalation. (Luck 1985; Woodward *et al.* 1986; Schulte-Hobein 1992) The findings of these studies generally agree than breast fed infants whose mothers smoke have a median urinary cotinine level 2-10 times higher than bottle fed infants exposed only via inhalation. Cotinine levels were related to number of cigarettes smoked by the mother as well as duration of nursing.

A large number of studies have measured nicotine and cotinine directly in breast milk with consistent findings related to smoking levels in the mothers. Diurnal variations depend on daily intake of milk and smoking pattern of mother. Exposure is modified by number of cigarettes smoked, depth of inhalation, time interval between smoking and nursing.

Luck (1985) found a 5-10 fold change in nicotine concentration in milk samples over a day. Studies by Jordanov (1990) found cotinine in amniotic fluid and the urine of neonates. Mean concentrations of cotinine in amniotic fluid were 15umol/l for unexposed non-smoking mothers, 25 umol/l in exposed non-smokers and 111umol/l in smoking mothers. Neonates of non-smokers exposed to ETS had significantly higher cotinine levels that neonates of non-smoking mother with no exposure.

DNA adducts, as a specific type of biomarker, provide valuable data in that adducts represent both markers of exposure and measures of a biochemical effect. Also, they have a longer half-life reflecting exposure over a longer period, usually about four months. In 1996, Denissenko demonstrated that DNA adduct formation due to exposure of human bronchial epithelial cells to benzo(a)pyrene diol epoxide resulted in strong and selective adduct

formation in the P53 gene associated with lung cancer. This study was understood to provide strong evidence of a direct etiological link between and specific carcinogen from tobacco smoke and a human cancer.

A report by Zenzes *et al.* investigated whether DNA adducts induced by benzo(a)pyrene were detectable in preimplantation embryos in relation to parental smoking. A total of 17 couples were categorized by their smoking habits (both partners smoked, neither smoked, etc). The 27 embryos of these couples were assayed using immunostaining of blastomeres specifically for B(a)P benzo(a)pyrene DNA adducts. This specific metabolite is the ultimate carcinogenic metabolite of benzo(a)pyrene. The mean intensity score of the staining was positively correlated with number of cigarettes smoked by fathers and results suggested that transmission of modified DNA was mainly through spermatozoa. As well, paternal transmission of modified DNA was confirmed by direct detection of DNA adducts in the spermatozoa of a smoking father and his embryo.

Cohort Studies

Neutel and Buck (1971) recorded smoking habits of mothers during pregnancy for 89,302 births registered at ten Canadian hospitals between 1958 and 1961 and all hospitals in England and Wales for a one week period. Data collected on 26% of the cohort was not utilized due to inability to definitively classify smoking level. The study found a small increased risk of childhood leukemia for smoking versus not smoking. (RR = 1.31, CI 0.8-2.2) The authors reported that there were few cases in the heavy smoking category and no evident dose response pattern.

Pershagen *et al.* (1992) assembled data from the Swedish Medical Birth Registry and the Swedish Cancer Registry to construct a cohort of 497,051 children born between 1982-1987. Cancer incidence was determined and compared to maternal smoking level at 2-3 months of pregnancy. The Swedish Medical Birth registry began collecting data on smoking in 1982, however due to logistical problems in the first year of collection, data was not available for all births in that year. A total of 327 cancers for which maternal smoking habits were known were analyzed, however no association was found for either all cancer combined or lymphatic and hematopoietic cancers combined. One major limitation to this study is that followup for cancer incidence stopped at age 5 years for all subjects. Therefore no assessment could be made of the effect of maternal smoking on cancers occurring at older ages. Golding *et al.* (1990) carried out a nested case control study on 16,193 children born in 1970 in the United Kingdom. The children were followed up at ages 5 and 10. Within the ten year period, 33 cancer cases were identified and three controls were selected for each case matched on factors such as maternal age at birth, parity and social class. Significantly more mothers of cases smoked five or more cigarettes per day throughout the pregnancy. (RR = 2.47, CI = 1.2-5.1)

Case Control Studies

Manning and Carroll conducted an early case control study examining parental smoking and the risk of childhood cancers in 1957. This was a hospital-based study of 188 children with acute leukemia. Children with orthopedic diseases were used as controls. Comparing smoking habits of the mothers of both groups, no difference was found.

Stewart *et al.* (1958) also looked at smoking habits in her study of children with cancer in England and Wales. With a total of 1,416 case control pairs, Stewart classified mothers and fathers as heavy, moderate, light or non-smokers. There was no effect for fathers however there was a small excess for smoking mothers (OR = 1.09, p=.04). However these results were not adjusted for confounders and the report warned that since the study was retrospective and at that time, mortality rates were much higher, smoking habits may have changed due to the effects of bereavement.

In Van Steensel Moll's 1985 study of 519 ALL cases in the Netherlands, no relation was found between disease and smoking or quantity of cigarettes smoked. Stjernfeldt (1986,1992) conducted a series of population based nationwide studies in Sweden. A total of 305 children under age 17 diagnosed with cancer from 1978 to 1981 were ascertained from the Swedish Child Leukemia Group. The control group consisted of 340 children with insulin-dependent diabetes mellitus. Information on smoking habits of the mother were obtained on 92% of the cases and controls. The study found an increased risk for mother's smoking during pregnancy which was confined to tumors of the reticuloendothelial system, primarily ALL. The increased risk persisted after adjustment for maternal age, birth order and parental occupation.

Buckley (1986) conducted a study of 1,814 children using data gathered by the US Children's Cancer Study Group and found no association between parental smoking and any types of cancer.

Ji *et al.* (1997) conducted a population based case control study in Shanghai looking at risk of childhood cancer in relation to a number of behavioral factors for 642 patients. In Shanghai, prevalence of smoking is high among men but extremely low among women. The

study found that paternal preconception smoking was related a significantly elevated risk of childhood cancers, particularly acute leukemia and lymphoma. For ALL, the risk rose with increasing pack-years of paternal preconception smoking with a trend p value of .01. Compared with children whose fathers had never smoked cigarettes, children whose fathers smoked more than five pack-years prior to their conception had adjusted OR's of 3.8 (95% CI = 1.3-12.3) for ALL risk.

Smulevich *et al.* (1999) found no relationship between parental smoking and risk of cancer in children. Parents were questioned about number of cigarettes smoked prior to conception but were not asked about smoking during pregnancy. Reluctance of parents to answer questions about "dangerous habits" was noted by authors. As well, interviews were retrospective and 96% of interviews were conducted with the mother only.

In summary, while there is currently inadequate accumulation of data on ETS and childhood leukemia risk to provide a foundation for conclusive evidence, there is reason for concern. Exposure characterization studies show that children are being exposed to tobacco smoke, most frequently in their homes. Children of parents with lower levels of education and income tend to be more highly exposed to household smoke. Biological studies have shown the constituents of ETS are present in body tissue of exposed children as well as in the breast milk of mothers. DNA adducts specific to benzo(a)pyrene have been detected in the spermatozoa of smoking fathers and their embryos. The results from epidemiological studies are inconsistent, with some studies reporting increased risk for parental smoking (Neutel and Buck 1971; Golding *et al.* 1990; Stewart *et al.* 1958; Stjernfeldt 1992; Ji *et al.*) and others reporting no effect (Pershagen *et al.* 1992; Manning and Carroll 1957; Van Steensel-Moll 1985; Buckley 1986; Smulevich *et al.* 1999)

2.2.5 Parental Alcohol Use

In a number of studies of risk of childhood leukemia or ALL, no consistent association has been found between maternal alcohol consumption before or during pregnancy. However, in three studies which were able to look at AML, a positive association with maternal alcohol consumption was found.

Severson *et al.* (1993) found that mothers who drank alcoholic beverages during pregnancy incurred an elevated risk (RR = 3.0, CI = 1.2 – 8.4) for their offspring. The risk was confined to children who were diagnosed with AML by age two. The increased risk was observed in each trimester. Although there was the suggestion of a dose-response relationship, the trend was non-significant.

Van Duijn *et al.* (1994) in a study involving 80 cases and 240 matched controls in the Netherlands, reported an increased risk for maternal alcohol use during pregnancy (RR = 2.6, CI + 1.4- 4.6). The risk was found for the 0-4 and 5-9 age groups, but not for the 10-14 age group. No increased risk was found for drinking in the year prior to the pregnancy by either parent. In the Shu *et al.* (1996) study of 88 cases of AML diagnosed in children aged 0 – 18 months, it was found that mothers who drank alcohol during pregnancy increased the risk of AML in their children. There was a dose response relationship with a significant trend ($p < .01$) With 1 – 20 drinks during the pregnancy, the relative risk was 2.4 (CI = 1.1 – 5.0) and with more than 20 drinks, the relative risk was 3.1 (CI = 1.2 – 8.1). The risk was not attenuated by adjustment for a number of other factors.

Father's alcohol consumption has never been shown to be associated with childhood leukemia.

2.2.6 Ethnic Origin

Data on ethnic origin and childhood cancer is not available from Canadian sources. The provincial cancer registries do not record ethnicity, nor do the hospitals collect these statistics. Ethnicity is also not recorded for deaths. (personal communication, Mary L. McBride, March 2000).

In the U.S., the highest rates of ALL are found in Hispanic, Filipino and Chinese populations (Linet and Devesa, 1991). The lowest rates are among blacks with an ALL incidence of about half that of whites. American Indians also have a lower rate than whites. American whites have a rate which is moderate to high by international standards.

Two studies in Britain (Stiller *et al.*, 1991; Powell *et al.*, 1994) found no significant differences in risk of ALL by ethnic status. These studies suffered from not using population-based ascertainment; from lack of population data by ethnic group; from lack of adjustment for socioeconomic status which is associated with both ethnicity and disease.

2.2.7 Ionizing Radiation

Ionizing radiation is one of the few known risk factors for childhood leukemia. A postive association between abdominal diagnostic radiation during pregnancy and subsequent childhood cancer was first reported by Stewart *et al.* (1958) in her study of 1,416 cancer cases aged 0- 9 in England and Wales. The study found "a large excess for direct foetal irradiation in the case series". Her work has been continued and is now known as the Oxford Survey of Childhood Cancers.

Stewart's study was criticized in subsequent years as having been subject to recall bias and spurious associations. A large number of studies were launched over the next twenty years in the wake of her findings. Court-Brown *et al.* (1960) found no association, however exposure event numbers were too small to be informative. In addition, there was lack of support from animal data; the absence of an association between childhood cancer and intrauterine exposure resulting from the atomic bomb explosions in Japan; the ongoing suspicion that some type of bias was in operation. (Monson and MacMahon (1984))

A few recent studies have reported positive findings. In a 1985 study Van Steensel-Moll reported an increased risk for ALL with prenatal exposure to X-rays. (OR = 2.2, CI + 1.2-3.8). All but one of these exposures were routine thoracic X-rays carried out in the first month of pregnancy. Smulevich's Moscow study reports three mothers of cases but no mothers of controls having had X-ray examinations during pregnancy.

Prenatal exposure to ionizing radiation is now considered to be a known risk factor for childhood leukemia. (Ries LAG *et al.* 1999) While many early studies found that intrauterine prenatal radiation is associated with a modest increased risk of leukemia and other types of childhood cancer, the relative risk has declined over time. This is compatible with a reduction in dose to the fetus with new technology and a reduced prevalence of exposure during pregnancy.

2.2.8 Summary

This literature review has surveyed both descriptive and analytical studies of childhood cancer and leukemia. Analytical epidemiological study designs applied to childhood leukemia included both case-control and cohort studies. Given that risk factors

remain unknown, many of these are exploratory and often a wide range of exposures are investigated for which there is no *a priori* hypothesis.

Despite remarkable achievements in the treatment of the childhood leukemias, there has been little impact on the incidence of the disease. ALL is the most extensively studied of the childhood leukemias, while the lack of analytic epidemiologic investigation of ANLL is a consequence of the small number of cases, with only 30 cases diagnosed annually in Canada. With the exception of exposure to in-utero ionizing radiation and the occurrence of Downs Syndrome, few risk factors have been demonstrated consistently over time and across studies. High birth weight, advanced maternal age and higher social class have been reported to be associated with childhood leukemia. However, findings have not been consistent, study methods have varied and most investigations have involved small numbers of subjects. The biologic foundation for the association remains unclear. While these are not causative variables, it is possible they are markers for underlying genetic, immunological or nutritional events.

In a recently published survey of factors investigated in relation to leukemia in children, Little (1999) classifies the factors discussed in this literature review according to their demonstrated degree of association. The survey considers intrauterine exposure to X-rays to be generally accepted as being associated with leukemia. High socioeconomic status and paternal smoking (with ALL) have been associated with leukemia with some degree of consistency. Factors for which evidence is inconsistent includes maternal smoking during pregnancy, paternal smoking (with all leukemias and ANLL), elevated maternal age and high birth weight. Maternal alcohol consumption is considered to be unlikely as a risk factor for

ALL, but suggestive for AML risk particularly for children diagnosed younger than three years of age.

In general, the studies reviewed share a number of problems. Early studies treated mortality as synonymous with incidence, but as improved treatment protocols began to enhance survival rates around 1970 studies which still used mortality as an outcome missed cases that survived. Many studies suffer from inadequate numbers of cases, especially when attempting to look at etiology by subtype or immunophenotype. Some studies are limited by less than full ascertainment of cases in jurisdictions without population based cancer registries. Although prospective uptake of cases in case control studies is becoming more usual, much data is based on retrospective ascertainment of cases. Especially when extended time periods are involved, this can enhance recall bias, reduce response rates and create problems in ascertaining a non-biased control group. In some studies, there is a lack of data collected on known and suspected confounders. Studies using a proportionate mortality approach could be affected by the relative frequency of other causes of death; this is especially the case in Third World countries. In fact, in developing countries, advances in treatment of communicable diseases and premature delivery may be an antecedent to the emergence of childhood cancer as a greater public health problem.

CHAPTER 3: METHODS

3.1 Overview

In view of the rarity of childhood cancer, most analytical studies attempting to elucidate etiology are designed as case-control studies. The data set for this thesis was a subset of data collected in the course of a 5 year multicentre, population-based case control study. The principal risk factor being examined was exposure to very low frequency (60 hz) electromagnetic fields, however data was collected on a wide variety of known and potential risk factors in the etiology of childhood leukemia.

The main study was a collaborative investigation conducted through the Canadian Cancer Registries Epidemiology Research Group (CCRERG) with the principal investigators based at the Cancer Control Research Programme at the British Columbia Cancer Agency (Mary McBride and Richard Gallagher) and the School of Occupational Health at McGill University (Gilles Theriault). The author of this thesis was the national study coordinator for the study.

3.2 Case Ascertainment

Cases were ascertained through cancer registries and pediatric oncology units in the participating provinces of B.C., Alberta, Saskatchewan, Manitoba. Quebec cases were ascertained through three Montreal area hospitals. All children aged 0 to 14, newly diagnosed with leukemia of any histological subtype from Jan. 1, 1990 to Dec. 31, 1994 (June 30, 1995 in B.C. and Quebec) and resident in the principal cities and surrounding areas of each province were eligible for inclusion in the study. All diagnoses were confirmed by pathology report. Deceased cases were included in the study, however children with a history of

Down's syndrome were excluded due to the association between Down's syndrome and leukemia. Ascertainment was retrospective for the first year of the study; subsequent cases were ascertained immediately upon diagnosis.

3.3 Control Ascertainment

For each participating case, one control was randomly selected from a population-based register, usually the provincial health plan. In Quebec, Family Allowance records were used for the first two years of the study. Controls were matched to cases on gender, province and age. Children up to two years old were matched within three months of the birthdate of the index child. Children between two years old and 15 years old were matched within 6 months of the birthdate of the index child.

If a potential control could not be contacted after a minimum of five attempts or declined to participate, another potential control was selected.

3.4 Data Collection

Initial contact was by letter followed within two weeks by a telephone call. Once consent was obtained, collection of data was conducted by means of a fixed format questionnaire administered face to face by a trained interviewer in the subjects' home. Interpreters were supplied for all subjects when no adult family member spoke English or French. Data was collected on 399 matched case control pairs for a total of 798 subjects.

Questionnaires from all centres were forwarded to the Cancer Control Research Programme office at the British Columbia Cancer Agency for review, coding and data entry. Disease coding utilized the International Classification of Diseases Revision 9. Occupation

and industry coding were carried out using the 1980 version of the Standard Occupational Classification and the Standard Industrial Classification. All other variables were coded using study-specific coding schemes.

3.5 Power

Original power calculations were carried out for each variable of interest employing an estimated relative risk of 1.7 (one sided, a = .05) for the target study population of 405 cases. The calculations yielded powers of: 82% power to detect differences for maternal age using a prevalence of .12 for mothers 40 years and older; 90% power to detect differences for birthweight using a prevalence of .15 for birthweight 4000 gm. and over; 97% power to detect differences for maternal education level using a prevalence of .37 for college or university level and 97% power to detect differences for paternal education level using a prevalence of .40 for college or university level education.

3.6 Classification of SES by Occupation

Occupations were grouped into four categories: high, intermediate and low socioeconomic status and homemakers. This approach conceptualizes occupations as a measure of socioeconomic position within the workforce. The distinctions are based on a graded hierarchy of occupations ranked according to skill.

The occupational categorizations were based on the first three digits of the Standard Occupational Classification (1980). The category designated as high SES included occupations in management, administration, natural sciences, engineering, mathematics, religion, teaching, medicine, health, arts, literature and recreation . The category designated

as intermediate SES included clerical, sales and services occupations. The low SES category included blue-collar occupations such as construction, fishing, logging, fabrication, pulp and paper processing and machining.

Parents reporting homemaker as their usual occupation were designated as a separate group with no specific ranking. No parents reported their usual occupation as student, unemployed or retired.

3.7 Analytical Methods

1. The frequency distribution of each variable among cases and controls was determined and examined for errors, unlikely values and inconsistencies.

2. A correlation matrix was developed to examine to what extent predictor variables were associated.

3. Odds ratios and 95% confidence intervals around leukemia risk were calculated for maternal age, birthweight, socioeconomic status and selected potential confounders using an unmatched analysis controlling for the original design variables of province, age group and gender.

4. A variable was defined as a potential confounder if it had an odds ratio of more that 1.5 (for a dichotomous exposure) and a significance level of less than .10 or a significance level of less than .05 regardless of its odds ratio. Therefore, factors with small odds ratios (<1.5) which were statistically significant were included in subsequent modeling.

5. The three primary risk factors and potential confounders and effect modifiers were examined in a multivariate logistic regression model using SPSS. Generally a matched design would call for a conditional logistic regression method for analysis, however since

cases and controls were not uniquely matched a logistic regression method was adopted. A comparison was done with a conditional model and the odds ratios were nearly identical.

6. Variables were submitted for logistic regression analysis in four separate models. Model 1 was comprised of variables related to SES; Model 2 was based on behavioural variables; Model 3 was concerned with demographic variables; Model 4 was based on variables that might indicate exposure to environmental tobacco smoke.

7. In each model the selected variables were subjected to backward and forward logistic regression procedures. The surviving variables from each model were the combined into a fifth model again utilizing forward and backward logistic regression.

CHAPTER 4: RESULTS

4.1 Participation Rates

A total of 399 case control pairs participated in the study. Details of subject response and participation are outlined in Table 1. Out of the 449 childhood leukemia cases ascertained during the study period, 4 could not be located, leaving a total of 445 eligible respondents. Of these, 399 consented to participate in the study giving a response rate of 90% for cases.

Table 1. Participation Rates

Participant Response Status	Case (n)	Case (%)	Control (n)	Control (%)
Potential subjects ascertained	449		675	
Could not find	4		149	
Total eligible respondents	445	100	526	100
Physician refusal	14	3	0	
Family refusal	29	7	116	22
Refusal for health reasons	0	0	7	1
Refusal due to language difficulty	3	<1	4	<1
Total refusals	46	10	127	24
Participating subjects	399	90	399	76

The number of potential controls ascertained was 675. Of these 149 could not be found, leaving 526 eligible respondents. Seventy-six percent of eligible respondents agreed to participate. Reasons for non-participation included the refusal of the treating oncologist to give permission to contact the family; refusal by the family themselves; health problems which prevented a family and/or child from participating; language differences that prevented even initial communication.

4.2 Characteristics of Participants

Comparative characteristics of study participants are described in Table 2. for gender; province of residence; age at diagnosis; household income; ethnic origin; parental age, education, occupational and smoking status. In Table 2., missing values are tabulated for each variable, however are excluded from the reported percentages. This convention is followed for all succeeding tables.

Table 2. Comparison of characteristics of participating cases and controls

Characteristic	Cases (n)	Cases (%)	Controls (n)	Controls (%)
Gender				
Female	196	49	196	49
Male	203	51	203	51
Missing	0		0	
Province				
British Columbia	105	26	105	26
Alberta	59	15	59	15
Saskatchewan	24	6	24	6
Manitoba	25	6	25	6
Quebec	186	47	186	47
Missing	0		0	
Age at dx or reference date				
<18 months	36	9	33	8
18 months to 4 years	190	48	188	47
5-9 years	105	26	113	28
10-14 years	68	17	65	16
Missing	0		0	
Household Income				
<$15,000	45	12	29	7
15-29,999	76	20	56	14
30-44,999	93	24	102	26
>45,000	175	45	208	53
Missing	10		4	

Table 2. (cont.)

Characteristic	Cases (n)	Cases (%)	Controls (n)	Controls (%)
Mother's Age				
< 25 yr.	96	24	64	16
25-29	153	39	136	35
30-34	112	28	134	34
>= 35	35	9	60	15
Missing	3		5	
Father's Age				
< 25 yr.	50	13	32	8
25-29	127	33	105	27
30-34	123	32	122	32
>= 35	89	23	127	33
Missing	10		13	
Mothers Education				
<8 yr	10	3	10	3
8-11 yr	63	16	47	12
High school	132	33	114	29
Tech\Vocational	85	21	80	20
College\University	99	25	122	31
Graduate Studies	10	3	26	7
Missing	0		0	
Fathers Education				
<8 yr	14	4	10	3
8-11 yr	77	20	55	14
High school	91	23	94	24
Tech\Vocational	83	21	78	20
College\University	96	25	120	31
Graduate Studies	30	8	37	9
Missing	8		5	
Mothers Occupational Status				
Low	38	10	26	7
Intermediate	197	50	157	40
High	91	23	137	35
Homemaker	71	18	77	19
Missing	2		2	

Table 2. (cont.)

Characteristic		Cases (n)	Cases (%)	Controls (n)	Controls (%)
Fathers Occupational Status					
Low		185	47	169	43
Intermediate		95	24	78	20
High		112	29	144	37
Homemaker		0	0	0	0
Missing		7		8	
Ethnic Origin					
Caucasian (all 4 grandparents)		290	79	316	85
Multiple origins		62	17	52	14
Asian (all 4 grandparents)		15	4	5	1
Missing		32		26	
Smoking Status					
Mother					
Smoked month before pregnancy	Yes	149	38	120	30
	No	246	62	273	70
	Missing	4		6	
Smoked during pregnancy	Yes	154	39	121	31
	No	241	61	272	69
	Missing	4		6	
Father					
Smoked month before pregnancy	Yes	185	48	151	40
	No	201	42	224	60
	Missing	13		24	
Smoked during pregnancy	Yes	187	48	161	42
	No	201	42	224	58
	Missing	11		14	

Study participants were matched by gender and age. For participants aged 0-2, matching was done within 3 months either side of the birthdate of the case. For participants aged 3-14, the matching criteria was within 6 months of the birthdate of the case. Therefore, by design, the gender and age distribution of cases and controls are very close.

The slight excess of boys in the study group (1.04:1) is slightly lower than, but consistent with published incidence figures for Canada. The reported incidence rate by gender for Canada from 1982-1991 for all childhood leukemias is 1.3:1 male:female (Parkin 1998).

Case age groupings are consistent with Canadian incidence figures. Parkin (1998) reported the following percentage breakdown for age groupings from 1982-1991. Age 0 = 5.5%; age 1-4= 48%; age 5-9= 26%; age 10-14=17%. This demonstrates that the ascertainment profile with regards to age matched the literature very closely.

In distribution of other factors, cases tended to have lower household incomes, be of Asian or multiple ethnic origins and have parents with lower educational credentials. The usual occupation of case parents was more often in a low or intermediate occupational category. The number of homemakers was similar among mothers of cases and controls. No fathers reported homemaker as their usual occupation.

More parents of cases smoked before and during the index pregnancy. In both case and control groups, for both parents, there was a greater number of smokers in the month before the pregnancy compared to smoking anytime during the pregnancy.

4.3 SES Variables

Data on social class in this study was collected primarily to control for socioeconomic position rather than to specifically study its effects. The variables available as measures of the socioeconomic position of the household were parental educational levels, occupational status of the parents and annual family income. It was assumed that these variables could be used as indicators of the child's socioeconomic resources relevant to disease status.

Results of the univariate analysis for socioeconomic variables are presented in Table 3. The pattern that emerges reveals a population of cases with lower levels of income, education and occupational status.

Table 3. Risk of childhood leukemia in relation to various SES indicators, adjusted for age and gender of child and province of residence.

SES indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Household Income						
<$15,000	45	29	1.00			
15-29,999	76	56	0.88	0.49-1.57	.65	
30-44,999	93	102	0.59	0.34-1.01	.06	
>45,000	175	208	**0.54**	**0.33-0.90**	**.02**	
						.003
Mothers Education						
<8 yr	10	10	1.00			
8-11 yr	63	47	1.33	0.51-3.48	.56	
High school	132	114	1.15	0.46-2.88	.77	
Tech\Vocational	85	80	1.06	0.42-2.68	.91	
College\University	99	122	0.80	0.32-2.03	.64	
Graduate Studies	10	26	0.38	0.12-1.20	.10	
						.002
Fathers Education						
<8 yr	14	10	1.00			
8-11 yr	77	55	1.74	0.68-4.47	.25	
High school	91	94	1.72	0.95-3.11	.08	
Tech\Vocational	83	78	1.19	0.68-2.09	.54	
College\University	96	120	1.30	0.73-2.31	.37	
Graduate Studies	30	37	0.98	0.56-1.70	.94	
						.014
Mothers Occup Status						
Low	38	26	1.00			
Intermediate	197	157	0.85	0.50-1.47	.57	
High	91	137	**0.45**	**0.26-0.80**	**.006**	
Homemaker	71	77	0.62	0.34-1.32	.13	

Table 3. (cont.)

SES indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Fathers Occup Status						
Low	185	169	1.00			
Intermediate	95	78	1.10	0.76-1.58	.61	
High	112	144	**0.71**	**0.51-0.98**	**.04**	
Homemaker	0	0				
						.05

Household income was reported at one point in time, usually one to two months after the diagnosis of childhood leukemia. Of course, this may fail to capture fluctuation of income prior to diagnosis, however of greater concern would be alteration in income post diagnosis as a direct result of the disease. With the lengthy treatment period for childhood leukemia, usually two years for girls and three years for boys, it is not uncommon for at least one parent to withdraw from employment. The prospective design of the study guarded against possible bias due to reverse causation such as the financial impact of disease on household income.

The uppermost level for reporting income was set at $45,000 per year. In retrospect, this may have been too low as 48 % of all subjects fell into this category. This means that any gradient of risk at income levels above $45,000 would necessarily be obscured and that it is difficult and inappropriate to propose an effect per unit change of income at higher levels.

Often questions about income tend to be sensitive and regarded as private and personal information by study participants. Non-response to questions about income can be high, however in this study, more than 98% of participants agreed to give information on annual income.

A gradient with a significant trend towards reduced risk with higher income was apparent in the analysis of household income. A household income of more than $45,000 per year was associated with a lower risk of leukemia (OR = 0.54, CI = 0.33-0.90, p = .02).

Of course, purchasing power and available income attributable to a certain level of household income will vary by the number of persons supported by that income and the province of residence. While participants were not directly asked about how many persons were supported by their income, provincial differences were minimized by the adjustment for province of residence within the analysis.

In this study, educational level was measured in terms of credentials rather than years of education on the basis that possession of a credential is a more meaningful indicator of potential socioeconomic positioning in the labour force. Education measures are generally stable over an adult lifespan, applicable to persons not in the active labour force such as homemakers and are not affected by external circumstance such as illness or job-loss. Data was collected on educational levels for both parents, allowing for a more detailed construction of socioeconomic position of the household in which the child resides.

The level of education attained by the mother showed a gradient that had a significant trend across levels of achievement ranging from an OR of 1.33 for less than a high school diploma to an OR of .38 for completion of graduate studies. No specific level of lower education was significantly associated with risk.

Paternal educational level showed similar results with a gradient of risk ranging from an OR of 1.74 for less than a high school diploma to an OR of .98 for completion of graduate studies. Again, no specific level of lower education was significantly associated with risk. The trend across categories was significant at a p value of .014.

Occupational status was classified by low, intermediate or high socioeconomic categories based on the usual occupation of each parent. For both parents, occupation in a high socioeconomic category was associated with lower risk. The effect for mothers was especially pronounced with an OR of .45 at a p value of .006. For fathers the OR was .71 with a p value of .04.

One of the difficulties with occupational status classifications is developing a method to include or account for persons who are outside the workforce such as students, homemakers, retirees etc. Using data on usual occupation rather than current occupation is helpful in this regard as it maximizes the number of participants who can be classified by occupation. Since this study was looking at families of young children, it was expected that the major group outside a traditional occupational classification would be homemakers. Mothers who reported their usual occupation as homemaker showed a non-significant lower risk with an OR of .62 when compared to the low occupational category. No fathers reported homemaker as their usual occupation.

The overall pattern of low socioeconomic status for cases is in contrast to some of the literature on childhood leukemia, but is consistent with population health literature showing an almost universal finding of disease being correlated with lower socioeconomic status (Evans *et al.*, 1994).

4.4 Behavioral Variables for the Mother

Detailed information was collected on the timing and levels of maternal smoking and alcohol use.

Table 4. presents the univariate analysis of behavioural variables of the mother such as alcohol and smoking use just prior to and during the pregnancy.

Table 4. Univariate analysis of mother's behavioural variables as risk factors for childhood leukemia, adjusted for age and gender of child and province of residence.

Behavioral Indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Mother						
Smoked during pregnancy no	241	272	1.00			
yes	154	121	**1.45**	**1.08-1.95**	**.01**	
Missing	4	6				
Month before, cig/day						
None	246	273	1.00			
< 10	29	22	1.48	0.83-2.66	.19	
10-20	57	47	1.36	0.89-2.09	.16	
>20	63	51	1.38	0.91-2.07	.13	.04
Missing	4	6				
Trimester 1, cig/day						
None	277	299	1.00			
< 10	33	27	1.33	0.78-2.27	.30	
10-20	53	33	**1.75**	**1.10-2.78**	**.02**	
>20	32	34	1.02	0.61-1.70	.94	.16
Missing	4	6				
Trimester 2, cig/day						
None	301	312	1.00			
< 10	22	22	1.04	0.57-1.93	.89	
10-20	47	30	**1.63**	**1.00-2.66**	**.05**	
>20	25	29	0.89	0.51-1.57	.70	.41
Missing	4	6				
Trimester 3, cig/day						
None	300	315	1.00			
< 10	23	21	1.15	0.63-2.13	.65	
10-20	47	30	**1.66**	**1.02-2.70**	**.04**	
>20	25	27	0.98	0.55-1.72	.93	.25
Missing	4	6				

Table 4. (cont.)

Behavioral Indicator		Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
During pregnancy, cig/day							
None		241	273	1.00			
< 10		68	54	1.44	0.97-2.15	.07	
10-20		62	38	**1.86**	**1.12-2.90**	**.006**	
>20		24	28	0.98	0.55-1.73	.93	.06
Missing		4	6				
Alcohol dur pregnancy	no	254	267	1.00			
	yes	141	126	1.16	0.87-1.58	.29	
Missing		4	6				
Month before, drinks/wk							
None		259	272	1.00			
1-2		78	54	**1.52**	**1.03-2.24**	**.04**	
>2		58	67	0.90	0.61-1.34	.62	.82
Missing		4	6				
Trimester 1, drinks/wk							
None		336	328	1.00			
1-2		39	38	1.00	0.62-1.60	.99	
>2		20	27	0.72	0.40-1.31	.29	.37
Missing		4	6				
Trimester 2, drinks/wk							
None		354	344	1.00			
1-2		31	32	0.94	0.55-1.57	.80	
>2		10	17	0.57	0.26-1.27	.17	.21
Missing		4	6				
Trimester 3, drinks/wk							
None		359	344	1.00			
1-2		26	32	0.77	0.45-1.33	.35	
>2		10	17	0.56	0.25-1.25	.16	.10
Missing		4	6				

Table 4. (cont.)

Behavioral Indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
During pregnancy, drinks/wk						
None	256	268	1.00			
1-2	118	97	1.27	0.92-1.75	.14	
>2	21	28	0.78	0.43-1.42	.42	.72
Missing	4	6				

There was a significant elevation of risk if mother smoked at all during the pregnancy (OR = 1.45, CI = 1.08-1.95, p = .01). Analysis of average cigarettes per day during the pregnancy showed that mothers who smoked 10-20 cigarettes per day were at a substantially increased risk of having a child with leukemia (OR = 1.86, CI 1.12-2.90, p = .006).

Elevated risk for smoking persisted when each trimester was examined separately. Once more, significantly elevated risk was confined to the 10-20 cigarette per week category for each trimester (OR = 1.75, CI = 1.10-2.78, p = .02; OR = 1.63, CI = 1.00-2.66, p = .05; OR = 1.66, CI = 1.02-2.70, p = .04 for the first, second and third trimesters respectively). The expected dose response relationship for levels of smoking was not in evidence for any period of the pregnancy. In this population, there is an apparently contradictory pattern of elevated risk for a moderate level of smoking with little or no excess risk at a high level of smoking. The reasons why risk is sequestered in this "mid" category may have a number of explanations and it is interesting to speculate on possible interpretations.

To begin with, pervasive public education on the inadvisabililty of smoking during pregnancy means there is an imperative on smoking mothers to temporarily stop or reduce smoking during pregnancy. This means that smoking levels during pregnancy are not representative of smoking patterns prior to pregnancy. Potential misclassification may result

when smoking status is based only on levels reported during pregnancy. Mothers in this study demonstrated the typical pattern of smoking reduction as pregnancy progressed. It is possible that a dose-response effect was obscured by a temporary reduction of smoking during pregnancy. Also, risk may still be present for the child since metabolite clearance is not immediate and early fetal development may be taking place in an embryotoxic environment. In fact, DNA adducts specific to tobacco smoke constituents are detectable for as long as four months after exposure (National Cancer Institute 1999).

Another factor to consider in explaining this seemingly contradictory result is that case families may have minimized their reporting of smoking due to a type of "socially unacceptable exposure" bias. With growing public education on the link between smoking and cancer, this may indeed have qualified as a sensitive question for parents of children with leukemia.

In addition, another related type of bias may have been at play in these results. The scale used to question parents on their smoking levels listed only three categories: less than 10 cigarettes/day; ten to twenty cigarettes; more than twenty cigarettes. The scale implies that 20 cigarettes or more per day is the "maximum" category. It is entirely possible that an "end of scale aversion bias" (Choi 1998) was operating preferentially for the parents of children with leukemia. It may have been advisable to devise a smoking scale with more gradation at the top end, perhaps up to 60 cigarettes per day, to minimize any aversion by parents to placing themselves at the top of the exposure range.

For both cases and controls, mothers tended to reduce their level of smoking as the pregnancy progressed. Many mothers who were smokers in the month prior to the pregnancy dropped to lower levels of smoking or stopped smoking completely during the gestational

period. Figure 1. documents the pattern of maternal smoking cessation across each trimester among previous smokers for cases and controls. For each trimester, the

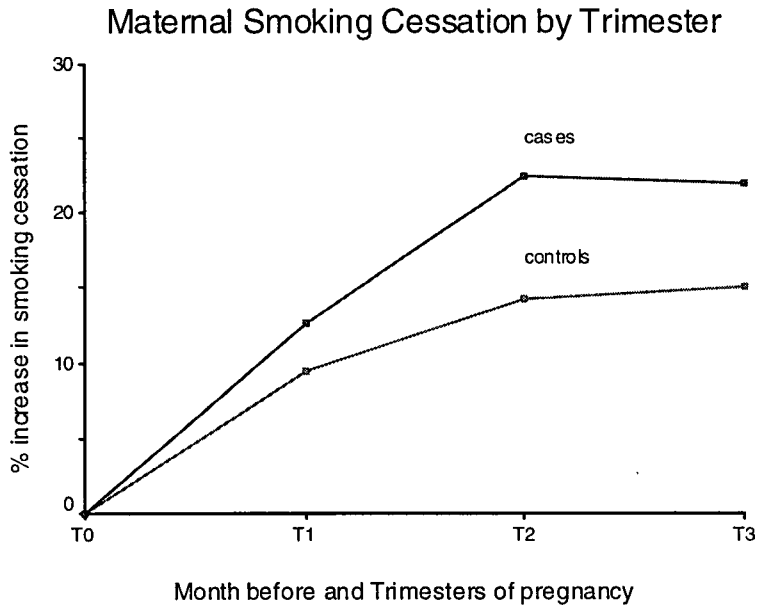

Figure 1.

percentage of previously smoking mothers (measured as smoking in the month prior to pregnancy) who had stopped smoking entirely is presented. Generally, the graph shows that the percentage of mothers who stop smoking increases with each trimester.

It is clear from Figure 1. that there was a difference between the case and control group in terms of maternal cessation of smoking through the trimesters. Twenty-two percent of case mothers who were smoking prior to the pregnancy had stopped smoking by the third trimester. For mothers of controls, that figure was only 15%. The difference is

intriguing given that case mothers were smoking in greater numbers and at higher levels than controls prior to pregnancy, yet reported a preferential cessation of smoking. This preferential reporting of smoking cessation by mothers of cases may signify a credibility gap and provide additional support for the previous interpretation of results with regard to elevated risk at moderate levels of maternal smoking.

The analysis of levels of alcohol use by mothers showed there was a statistically significant risk of disease if mothers drank one to two drinks per week in the month before the pregnancy. No risk was evident with drinking during pregnancy. In fact, the gradient ran in a contrary direction to expectation showing less risk with more than two drinks per week ($p = .06$). Again, there may have been stigma for reporting alcohol use during the pregnancy, but not before.

4.5 Behavioural Variables for Father and Parents Combined

The univariate analysis of behavioural variables for fathers in the study showed that for fathers smoking 10-20 cigarettes per day prior to pregnancy, there was a significant elevated risk of leukemia (OR = 1.69, CI = 1.06-2.69, $p = .03$). This result affords some support to evidence from other studies of a role for tobacco smoke exposure acting via mutation to paternal gametes as a risk factor for leukemia in the offspring. As further outlined in Table 5., there was elevation of leukemia risk for all levels of paternal smoking during every trimester of the pregnancy, however none of these parameter estimates attained statistical significance. As with maternal smoking, examination of levels of paternal smoking by trimester demonstrated no evidence of a dose response relationship at any period during the pregnancy. Fathers exhibited the same pattern of tending to reduce smoking

during the pregnancy, albeit in a more attenuated fashion than maternal reduction of smoking.

Table 5. Univariate analysis of father's behavioural variables as risk factors for childhood leukemia, adjusted for age and gender of child and province of residence.

Behav Indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Father						
Smoked during pregnancy no	201	224	1.00			
yes	187	161	1.30	0.98-1.73	.07	
Missing	11	14				
Prior to pregnancy , cig/day						
None	201	224	1.00			
< 10	23	20	1.29	0.69-2.41	.43	
10-20	53	35	**1.69**	**1.06-2.69**	**.03**	
>20	109	96	1.29	0.92-1.80	.14	.06
Missing	13	24				
Trimester 1, cig/day						
None	201	224	1.00			
< 10	20	16	1.39	0.70-2.76	.34	
10-20	46	32	1.60	0.98-2.61	.06	
>20	103	93	1.25	0.88-1.75	.21	.10
Missing	29	34				
Trimester 2, cig/day						
None	201	224	1.00			
< 10	20	15	1.49	0.74-2.98	.27	
10-20	41	31	1.46	0.88-2.42	.14	
>20	100	90	1.25	0.89-1.77	.20	.12
Missing	37	39				

Table 5. (cont.)

Behav Indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Trimester 3, cig/day						
None	201	224	1.00			
< 10	20	15	1.49	0.74-2.98	.26	
10-20	41	31	1.46	0.88-2.43	.14	
>20	102	90	1.28	0.91-1.81	.16	.10
Missing	35	39				
During pregnancy, cig/day						
None	201	224	1.00			
< 10	28	19	1.64	0.89-3.05	.11	
10-20	42	31	1.50	0.91-2.48	.11	
>20	101	90	1.27	0.90-1.79	.18	.11
Missing	27	35				
Alcohol dur pregnancy no	141	140	1.00			
yes	247	246	1.00	0.74-1.34	.99	
Missing	11	13				
1 Year prior, drinks/wk						
None	141	140	1.00			
1-3	76	68	1.11	0.74-1.66	.61	
4-7	59	65	.90	0.59-1.38	.63	
8-14	54	56	.96	0.62-1.49	.85	
>14	54	55	.98	0.63-1.52	.92	.74
Missing	13	15				
Parents smoke during preg						
Neither	156	187	1.00			
Father only	83	83	1.21	0.84-1.76	.31	
Mother only	44	37	1.45	0.89-2.37	.14	
Both	104	78	**1.62**	**1.12-2.33**	**.01**	**.007**
Missing	12	14				
Parents alcohol during preg						
Neither	118	122	1.00			
Father only	132	140	0.98	0.69-1.38	.89	
Mother only	22	18	1.25	0.64-2.46	.52	
Both	115	106	1.12	0.78-1.61	.55	.45
Missing	12	13				

When analyzed in isolation, fathers smoking during pregnancy did not materialize as a significantly elevated risk factor. However, one of the most striking findings in the analysis of the behavioural variables is that when maternal and paternal smoking status during pregnancy are combined into one variable, there is a significant increase in risk. (OR = 1.62, CI = 1.12-2.33, p = .01) if both parents smoked during the pregnancy.

With both parents smoking, the possible routes of exposure include a multiple of direct and indirect exposures including effects on parental gametes, exposure via breast feeding and environmental tobacco smoke.

Alcohol use by the father before or during pregnancy does not contribute to risk in this analysis. Examination of alcohol use for both parents combined shows a slight non-significant elevation in risk when both parents drink. This is likely driven by the elevated risk shown for maternal alcohol use before and during pregnancy.

4.6 Birthweight, Gestational Period and Demographic Variables

Analysis at the univariate level for such variables as birthweight, gestational period, maternal age and child's ethnic origin are summarized in Table 6.

Table 6. Univariate analysis of demographic variables as risk factors for childhood leukemia, adjusted for age and gender of child and province of residence.

Indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Mothers Age						
<25 yrs.	96	64	1.00			
25-29	153	136	**2.62**	**1.55-4.44**	**.0003**	
30-34	112	134	**1.96**	**1.21-3.16**	**.006**	
>=35	35	60	1.43	0.88-2.33	.15	**.0001**
Birthweight						
< 2500 g.	23	17	1.45	0.75-2.81	.27	
2500 – 3499	192	206	1.00			
3500 – 3749	88	80	1.18	0.82-1.70	.37	
> 3750	95	94	1.08	0.76-1.54	.65	
Missing	1	2				
Gestational Period						
<=36 weeks	26	23	1.19	0.63-2.22	.59	
37-39 weeks	97	102	1.00			
40-41 weeks	218	222	1.03	0.73-1.45	.84	
>=42 weeks	54	50	1.14	0.71-1.83	.59	
Missing	4	2				
Ethnic origin of child						
Caucasian	290	316	1.00			
Other	77	57	**1.49**	**1.02-2.17**	**.04**	
Caucasian	290	316	1.00			
Other-non Oriental	59	44	1.47	0.96-2.25	.07	
Oriental (1 grandparent)	18	13	1.53	0.73-3.18	.25	
Caucasian	290	316	1.00			
Other-non Oriental	62	52	1.31	0.88-1.96	.18	
Oriental (4 grandparent)	15	5	**3.31**	**1.19-9.23**	**.02**	

High birthweight is generally considered to be a factor for which evidence of leukemia risk is suggestive, but not conclusive (Ries, 1999). In this study, birthweights were grouped into four categories. Using a birthweight of between 2,500 and 3,499 gm. as the

reference category, the results showed that low birthweight of less that 2,500 gm. carried a non-significant elevation in risk for leukemia (OR = 1.45, CI = 0.75-2.81, p =.27). Higher birthweights carried small, non-significant elevations in risk.

The analysis for mother's age at birth showed a significant effect of higher risk for mothers of younger age. Using mothers less than 25 years old as the reference group, risk declined with age group. The trend across categories was highly significant (p = .0001). Risk estimates for each age category were as follows: for the 25 – 29 year old age group (OR = 2.62, CI = 1.55-4.44 p = .0003); for the 30 - 34 age group (OR = 1.96 CI = 1.21-3.16, p = .006); for the 35+ age group (OR = 1.43, CI = 0.88-2.33, p = .15). These results are contrary to the majority of findings in the scientific literature, however are supported by the findings of Fasal *et al.* (1971) where risk for mothers over age 40 was lower than the level for the youngest age group. As well, it is not clear that studies with positive findings for advanced maternal age and leukemia risk excluded Down's Syndromes cases from their enrollment. Down's Syndrome is known to be highly associated with both advanced maternal age and leukemia risk (Little 1999).

There was no significant effect of gestational period on risk of disease. A reference category of 37– 39 weeks was used to compare risk with gestational periods of less than 36 weeks, 40-41 weeks and 42 weeks or more. Gestational periods lasting 42 weeks and longer or less than 36 weeks were associated with non-significant elevated risks with odds ratios of 1.14 and 1.19 respectively.

Ethnic origin is never a straightforward variable for at least two reasons. Firstly, there are a variety of ethnic groups that do not fit easily into categories. Secondly, it is difficult to categorize in a simple fashion individuals with ancestors in more than one group. In this

study, ethnic origin for each child was collected by asking the origin of each grandparent. Ethnic origin was then analyzed using three separate methods. The first analysis was dichotomous for Caucasian versus non-Caucasian and demonstrated that being of an ethnic origin other than Caucasian carried a risk with an OR = 1.49, (CI = 1.02 – 2.17, p value = .04). The second analysis integrated a category of one grandparent of Oriental origin. The odds ratio for risk increased to 1.53, however did not attain significance. The third analysis included a category with all four grandparents of Oriental origin. When Oriental origin was concentrated in this fashion, the demonstrated risk increased, with an OR = 3.31, (CI = 1.19-9.23, p value = .02).

There is no straightforward explanation for the finding of increased risk for Oriental origins in this population. In entertaining the possibility of genetic susceptibility, it would be instructive to review incidence rates from the country of origin to see if this might be a "carry-over" effect. However data on incidence rates from China and Hong Kong are not helpful. The Hong Kong registry reports a crude rate of childhood leukemia of 5.24 per 100,000 which is indeed higher than Canada's crude rate of 4.8 per 100,000 (Parkin 1998). In Hong Kong, cancer notification is on a voluntary basis, which may lead to under-reporting. However the registry itself publicized it's own concerns about overascertainment (Parkin 1998).

> "Some incidence rates, notably for leukemia, are rather high, possibly because of undetected duplicate registrations. This could have arisen because children have no identity cards, creating difficulties in cross checking. Chinese parents may change the child's name after the diagnosis of cancer believing this may bring better luck to the child."

The only registry in mainland China, the Tianjin Cancer Registry reports a crude childhood leukemia rate of 4.02 per 100,000 and states that physicians and medical clerks are

obliged to notify the registry of cancer diagnoses (Parkin 1998). Complicating the attempt to interpret differentials in incidence rates is the fact that Canadian registries and hospitals do not collect data on ethnic origin.

Higher rates in children of Oriental origin may also be related to socioeconomic status. The possibility of differential rates of consenting to participate in the study in case versus control groups also cannot be discounted.

4.7 Mother's X Ray Exposure Variables

Given that X ray exposure in utero is one of the few known risk factors for childhood leukemia, a number of variables relating to mother's medical exposure to ionizing radiation were appraised. Table 7 summarizes the results of the univariate analysis for maternal X ray exposure.

Table 7. Risk of childhood leukemia in relation to mother's x-ray exposure, adjusted for age and gender of child and province of residence.

X ray indicator	Cases (n)	Controls (n)	OR	95% CI	P value
Xray 2 yr before preg.					
None	283	290			
Any	83	87	0.98	0.70-1.4	.93
Missing	33	22			
Xray month before preg.					
None	358	373			
Any	4	2	2.06	.38-11.3	.40
Missing	37	24			
Xray during preg					
None	369	365			
Any	20	27	0.74	0.40-1.3	.31
Missing	10	7			

Table 7. (cont.)

X ray indicator	Cases (n)	Controls (n)	OR	95% CI	P value
Xray pelvimetry dur preg					
None	385	377			
Any	10	16	0.61	0.27-1.37	.23
Missing	4	6			
Therapeutic Xrays					
2 yr prior to preg					
None	362	373			
Any	0	2			
Missing	37	24			
Month before preg					
None	362	375			
Any	0	0			
Missing	37	24			
During preg					
None	389	391			
Any	0	0			
Missing	10	8			
Pelvimetry dur. preg					
None	395	393			
Any	0	0			
Missing	4	6			

There was no indication on increased risk in the analysis of mother's exposure to ionizing radiation from two years prior to pregnancy and throughout the pregnancy. For x-rays taken in the month before the pregnancy there was a non-significant elevated odds ratio however, this was based on very small numbers. There were no reported therapeutic x-rays during the pregnancy.

Early studies, showed a consistent increased risk of leukemia associated with prenatal exposure to ionizing radiation with odds ratios in the area of 1.5. This risk factor is not

apparent in the results of this study. Due to low prevalence of exposure and technological improvements in x-ray equipment, medical exposure to ionizing radiation is unlikely to be an important current risk factor for leukemia.

4.8 Parental Occupation

Occupation was looked at initially and primarily as an element of social class. However, given the results of the parental smoking analysis, an exploratory analysis of parental occupation was undertaken. Occupations with a high likelihood of exposure to passive or active smoking were selected and submitted to univariate analysis. Some intriguing patterns of potential exposure emerged from this analysis and the results are presented in Table 8.

Table 8. Univariate analysis of parents' usual occupation as a risk factor for childhood leukemia, adjusted for age and gender of child and province of residence.

Usual Occupation in Service Industry	Cases (n)	Controls (n)	OR	95% CI	P value
Father					
Services	35	24	1.50	0.87-2.58	.14
Food beverage services	17	7	**2.48**	**1.01-6.06**	**.05**
Chefs and Cooks	11	4	2.78	0.88-8.82	.08
Mother					
Services	48	30	**1.69**	**1.04-2.72**	**.03**
Food Beverage Services	20	9	**2.29**	**1.03-5.09**	**.04**
Hairdressers	16	8	2.05	0.87-4.85	.10

Occupations were selected based on a combination of high potential for exposure to tobacco smoke as well as sufficient numbers within the study to afford meaningful analysis. Occupations within the service industry met both these criteria. Restaurants, bars and

nightclubs have been one of the last sectors of the economy to restrict smoking in the work environment and customers often frequent these establishments precisely because they are one of the few public arenas where smoking is acceptable. The reference category used for comparison purposes was all other occupations within the dataset. This method of comparison is consistent with other occupational analyses carried out at the B.C. Cancer Agency. Usual occupation was chosen as the occupational variable that would represent the broadest measure of potential exposure, however, this variable does not necessarily overlap temporally with the period of pregnancy.

The services category is an umbrella group which includes such groups as food and beverage services, personal services, protective services and clothing services.

The food and beverage services category includes occupations concerned with providing food and beverage catering services, cooking and preparing food, mixing and dispensing alcoholic drinks, arranging dining accommodation; receiving clients; serving food and beverages; and performing other related activities. It does not include food processing or managers of food service establishments. Chefs and cooks form a subgroup within the food and beverage services category. Hairdressers are a subgroup of the personal services category within the overall service industry grouping.

For fathers, usual employment in the services group was associated with increased risk of disease (OR = 1.50, CI = 0.87 – 2.58) which did not attain significance. Employment in the subcategory of food and beverage services group was associated with a significantly elevated risk (OR = 2.48, CI = 1.01 – 6.06, p = .05). Employment as a chef or cook was associated with a non-significant increased risk (OR = 2.78, CI = 0.88 – 8.82, p = .08).

The results for the analysis of maternal occupational variables were similar to the paternal results. Usual employment in the services group resulted in a significant elevation of risk (OR = 1.69, CI = 1.04 – 2.72, p = .03). As with fathers, usual occupation within the sub category of food and beverage services shows a significantly elevated risk (OR = 2.29, CI = 1.03 – 5.09, p = .04). There was a non-significant elevated risk of childhood leukemia with usual maternal occupation as a hairdresser (OR = 2.05, CI = 0.87-4.85, p = .10).

4.9 Model Summary

Four models encompassing variables related to different areas of risk were assessed using logistic regression techniques. Variables were chosen for each model based on results of the univariate analysis. Those that remained in the equation following forward and backward logistic regression analyses for each model were combined into a final risk model.

Table 9. Summary of Models 1-5: Multivariate analysis using forward/backward stepwise logistic regression adjusted for age group, gender and province.

Variables in each model selected from univariate analysis	OR	95% CI	P value
Model 1: SOCIO-ECONOMIC STATUS			
Mother's Education			
Household Income			
<$15,000	1.00		
15-29,999	0.70	0.37-1.30	.25
30-44,999	**0.47**	**0.26-0.85**	**.01**
>45,000	**0.50**	**0.28-0.87**	**.01**

Table 9. (cont.)

Model 2: BEHAVIOUR	OR	95% CI	P value
Mother's SES by Occupation			
Low	1.00		
Intermediate	0.84	0.48-1.48	.55
High	**0.49**	**0.27-0.88**	**.01**
Homemaker	0.58	0.32-1.08	.08
Mother cig/day dur preg			
None	1.00		
< 10	1.38	0.92-2.08	.12
10-20	**1.98**	**1.26-3.13**	**.003**
> 20	0.99	0.55-1.79	.97
Father cig/day dur preg			
Mother drinks/week, month before preg			
None	1.00		
1-2	1.48	0.99-2.20	.05
>2	0.85	0.56-1.29	.44
Model 3: DEMOGRAPHICS			
Ethnic origin			
Caucasian	1.00		
Other-non Oriental	1.30	0.86-1.96	.20
Oriental (4 grandparent)	**3.56**	**1.27-9.99**	**.02**
Mother's age			
<25 yrs.	1.00		
25-29	0.73	0.49-1.1	.13
30-34	**0.56**	**0.37-0.86**	**.008**
>=35	**0.40**	**0.23-0.69**	**.001**
Model 4: ENVIRONMENTAL TOBACCO EXPOSURE			
Mother: cig/day dur pregnancy			
None	1.00		
< 10	1.42	0.94-2.13	.10
10-20	**1.99**	**1.26-3.14**	**.003**
> 20	0.99	0.55-1.79	.98

Table 9. (cont.)

Model 4: ENVIRONMENTAL TOBACCO EXPOSURE	OR	95% CI	P value
Father: food and bev.serv. 13B			
No			
Yes			
Mother: food and bev.serv 13B			
Father: cig/day prior to pregnancy			
Model 5 COMBINATION OF MODELS 1-4			
Mother's Age			
Ethnic Origin			
Caucasian (all 4 grandparents)	1.00		
Multiple Origins	1.38	0.91-2.09	.13
Asian (all 4 grandparents)	**3.65**	**1.27-10.52**	**.02**
Mother cig/day dur pregnancy			
None	1.00		
< 10	1.45	0.94-2.23	.09
10-20	**1.80**	**1.12-2.90**	**.02**
> 20	0.90	0.47-1.72	.75
Income			
Mother's SES by occupation			
Low	1.00		
Intermediate	0.87	0.48-1.54	.62
High	**0.48**	**0.26-0.88**	**.02**
Homemaker	0.64	0.34-1.22	.17
Mother drinks/week, month before preg			
None	1.00		
1-2	**1.77**	**1.17-2.70**	**.007**
> 2	0.84	0.55-1.30	.44

Model 1 was based on variables related to social class including household income; level of education for both parents and socioeconomic status based on occupation for both parents. Household income and mothers occupational status, both protective at higher levels, were retained in the model. Risk estimates were similar to the univariate analysis (OR = 0.50, CI = 0.28-0.87 for highest level of income; OR = 0.49, CI = 0.27-0.88 for highest level of occupational status).

Model 2 employs behavioural variables from both parents to predict risk including mothers level of smoking during pregnancy; father's level of smoking during pregnancy; parents combined smoking status during pregnancy and mother's level of alcohol use in the month before pregnancy. The Model 2 variables selected were mother's level of smoking during pregnancy (OR = 1.98, CI = 1.26-3.13 for mid-level of smoking) and mother's level of alcohol use in the month before pregnancy. Surprisingly, the risk estimates for alcohol use did not attain significance even though this variable survived the backward (but not in the forward) logistic regression analysis.

Ethnic status and mother's age were defined as demographic variables for Model 3. Both variables were retained in the analysis. Risk estimates for ethnic origin (OR = 3.56, CI = 1.27-9.99 for four Asian grandparents) and mothers age (OR = 0.40, CI = 0.23-0.69)

Model 4 attempted to assemble variables related to the influence of environmental tobacco smoke on a child's risk of disease. The level of mother's cigarette smoking during pregnancy, employment in the service industry, and parents smoking status during pregnancy may give some indication of the exposure of the fetus to tobacco smoke or the metabolites of smoking. Father's smoking prior to pregnancy as well as employment in the service industry may be related to mutational effects on gametes at time of conception. As well, mother's

level of smoking during pregnancy is likely to be at least as high as mother's smoking after pregnancy, thus providing some clue to the likelihood of exposure to the child through breastfeeding. It is assumed that parental smoking can be used as a surrogate for the child's exposure to environmental tobacco smoke, however parents were not questioned whether their smoking took place inside or outside the family home. Also, the children were not questioned about their own smoking habits. Given the maximum age for inclusion was 14, and that the 10-14 year age group accounted for less than 17% of participants, it is not likely that many children had a significant self-exposure to tobacco smoke.

Two variables were retained in this analysis. The level of mother's smoking during pregnancy (OR = 1.96, CI = 1.24-3.11 for mid level of smoking) was retained for this model and for model 2 as well. Employment of the father in the food and beverage service industry survived backward regression, though not attaining significance (OR = 2.35, CI = 0.96-5.80).

The surviving variables from Models 1 – 4 were combined and assessed in a final logistic model. Risk estimates of variables remaining in Model 5 were Asian ethnic origin, (OR = 3.65, CI = 1.27-10.52, p value = .02); mother smoking 10-20 cigarettes per day during pregnancy, OR = (1.80, CI = 1.12-2.90, p value = .02); mother's usual occupation in high SES category, OR = 0.48, (CI = 0.26 – 0.88, p value = .02); mother's alcohol use of 1-2 drinks per week in the month before pregnancy, OR = (1.77, CI = 1.17 – 2.70, p value = .007).

The final model was reanalyzed using the same forward and backward logistic regression techniques on a data set that excluded all records with missing values for any of the variables considered in Models 1-4. This method arrived at the same final model and produced no appreciable differences in any of the parameter estimates.

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 Overview

This thesis examined maternal age, birthweight, social class and other potential risk factors in relation to risk of childhood leukemia using data collected via personal interview with parents in a large case control study with excellent response rates. Univariate analysis showed a case group with lower maternal age at birth, lower levels of parental occupational status, education and household income. There was no evidence of a significant effect for birthweight on disease risk. Ethnic status was shown to be a significant risk factor at the univariate level with excess risk for Orientals. Ionizing radiation, one of the few known risk factors for childhood leukemia was not shown to be an important risk factor in this analysis, likely due to low prevalence and levels of exposure.

The univariate analysis revealed a collection of elevated risk factors related to tobacco smoke. Statistically significant excess risk was found for: any maternal smoking during the pregnancy; maternal smoking of 10-20 cigarettes per day in any trimester; maternal smoking of an average of 10-20 cigarettes per day during the pregnancy; paternal smoking of 10-20 cigarettes per day prior to the pregnancy; both parents smoking during the pregnancy and employment of either parent in the food and beverage service industry as their usual occupation. Other behavioural risk factors of interest included a significant excess risk for maternal alcohol use of 1-2 drinks per week in the month prior to the pregnancy.

Significant risk factors from the univariate analysis were assembled into four models based on putative areas of risk. The spheres of risk encompassed within each model were socioeconomic status; behavioural factors, demographics and exposure to environmental tobacco smoke. The four models were assessed separately using logistic regression

techniques and then combined and assessed in a final logistic model. The variables which persisted into the final model and were shown to confer excess risk were: Oriental ethnic origin; low maternal occupational status; maternal smoking of 10-20 cigarettes per day during pregnancy and maternal alcohol use of 1-2 drinks per week prior to pregnancy.

5.2 Interpretation of Final Model

The final model shows statisically independent effects on risk of childhood leukemia for each of the four parameter estimates in the model. The behavioural variables which persisted into the final model, maternal smoking and alcohol use, are usually associated with low socioeconomic status. Low maternal occupational status is, by definition associated with low socioeconomic status. Oriental ethnic origin is likely associated with lower socioeconomic status. The odds ratios of all these parameter estimates increased from the univariate to the multivariate analysis with the exception of the maternal smoking variable which was reduced slightly from 1.86 to 1.80. The main challenge of interpreting these results lays in the ability to distinguish between the *indirect effects* of behavioural and demographic factors as relayed through the socioeconomic variables and the *direct effects* which occur through some alternate pathway for which the intermediates may be suspected but remain unidentified and unmeasured.

5.3 Relationship between social class and behavioural variables

The relationship between social class and behavioural or demographic variables is complex. Socioeconomic status is a composite attribute influenced by genetics, culture,

exposures, individual physiological responses and is therefore difficult to assess as a single risk factor.

There are three pathways to be considered in how these factors may be operating to increase disease risk. Firstly, the behavioural variables such as smoking and alcohol use may indicate a direct biological effect that increases risk of disease. The ethic origin variable may also be acting directly through genetic susceptibility to cause disease. Secondly, the behavioural/demographic variables acting indirectly on disease risk through their association with socioeconomic status. The third possibility is that socioeconomic status itself acts directly on disease risk through a biobehavioural process which alters immune function as a structural responses to stress.

In the particular case of the child's exposure to environmental tobacco smoke, it would be valuable to understand to what degree socioeconomic status is measuring unobserved exposure to ETS and to what degree ETS exposure is measuring unobserved socioeconomic status. There may be a public health concern to be considered with this particular exposure. Although definitive conclusions regarding causality cannot yet be made on the basis of available data, this thesis has found suggestive evidence that maternal smoking during pregnancy and other tobacco-related exposures may be a risk factor in the etiology of childhood leukemia. Data on DNA adducts provides some biological plausibility. The strength of the association is relatively high with an OR in the final model of 1.80 (CI = 1.12-2.90, p = .02) and there is a moderate overall consistency of findings among studies which have looked at this question.

While the design of this study does not allow for the necessary distinctions to be drawn which would identify the specific pathway(s) by which significant risk factors are

operating, this is not an unusual result. Kaufmann (1999) states that "by their very nature, social variables are difficult to interpret. The particular nature of social variables leads to numerous methodologic, substantive and logical problems, many of which remain unresolved in the literature and which therefore require further innovation and development".

5.4 Response Bias

As in any case control study, the possibility of response bias operating to influence findings must be seriously considered. In this study, both case and controls were selected from the same population base for every province. Possible effects through uneven participation by socioeconomic status cannot be entirely set aside. The control group may have been of higher socioeconomic status because they had the leisure time to participate or were more interested in participating because of higher educational levels. As well, controls of Chinese origin may have been more reluctant to participate.

5.5 Limitations

1. As with any epidemiological research, one of the major limitations of this study is the potential for uncontrolled confounding by events not accounted for in the data set.

2. Recall bias must also be considered as a possible limitation of any case control study since the outcome has preceded data collection. The primary variables under consideration in this thesis, (maternal age, birthweight and social class) are among the least likely to be subject to recall bias, since none involve exposures generally known to be risk factors. However, the behavioural variables may be influenced by recall bias as smoking and alcohol use are

commonly acknowledged to be risk factors for a variety of diseases and are actively discouraged during pregnancy by public health campaigns.

3. Careful attention must be given to selection bias and participation bias as these can be major unmeasured influences in case control studies. The population-based design of this study in combination with random selection methods should have minimized any faulty selection of cases and controls. Participation bias is less amenable to control by study design and may have been an operative factor in this study. The participation rate was excellent for cases (90%) and relatively good for controls (76%), however these rates are based on contactable potential subjects.

4. Misclassification due to end of scale aversion bias may have been influential in shifting risk estimates to lower levels of intake in the maternal smoking results.

5. Analysis of socioeconomic status by income was curbed by the absence of categories above $45,000 per annum; more categorization at the higher levels would have allowed for the construction of a gradient for upper income levels.

6. Given the multi-centre design of the study, the possibility of unequal recording of events by different observers must be considered. However, all interviewers received training and a standardized questionnaire was employed to minimize possible differences in data collection by interviewers.

5.6 Future Directions

The purpose of analytic studies of rare disease is to provide etiologic information by documenting the presence of associations between specific characteristics or environmental exposures and the outcome of interest.

If exposure to ETS is important in the etiology of childhood leukemia, it is an important public health imperative to look at the overall trend in smoking prevalence among population subgroups. It has been reported that age of starting smoking has been declining for females and that smoking initiation is more and more confined to the least educated females. As a result, the differential risk of ETS exposure to children may be shifting because of a shift in smoking patterns. Overpeck (1991) found that higher exposure to ETS is associated with families of low income and mothers with lower levels of education. One might also ask whether these young women have higher than average birth rates and because of low levels of employment spend more time with the developing child.

Despite the decreasing prevalence of ETS exposure to non-smokers in Canada due to increasing restrictions on smoking in the workplace and public locations, this will not affect children as the prime location for exposure for children is in the home. The timing and routes of infant exposure to tobacco smoke constituents are unique in that infants can be exposed prenatally if the mother smokes or is exposed to ETS during pregnancy. Postnatal exposure may occur directly through inhalation or indirectly via breast feeding. The small body weight of children relative to dose is also a consideration in assessing exposure.

The associations which have emerged in this thesis should be followed up in more focused investigations. Further analysis which might help in drawing a distinction between indirect risks relayed via socioeconomic status and direct risk via environmental tobacco smoke would be to look at parental smoking and occupational patterns by leukemia subtype, specifically ALL, to see if odds ratios intensify when risk is analyzed with a view towards cell type specific determinants of childhood leukemia. As well, it would be valuable to look at duration of mother's breastfeeding in relation to maternal smoking to assess whether direct

exposure through breastmilk confers excess risk. The literature suggests that the finding demonstrating excess risk for maternal alcohol use prior to pregnancy should be followed up by looking specifically at AML.

Future inquiry into this area should include a more detailed history on maternal daily smoking patterns. Questions on number of cigarettes smoked, depth of inhalation, frequency of smoking prior to nursing, interval between last cigarette smoked and nursing, and maternal exposure to ETS from other household members. Pattern of paternal smoking may be important prior to pregnancy and as ETS exposure during and post pregnancy. This level of detail would be best addressed in a cohort design, but given the large numbers of participants required for sufficient power, a cohort design would likely be impractical as well as prohibitively expensive.

The etiology of childhood cancer is a complex field, requiring thoughtful investigation into biological, quantitative and social dimensions. The unequal burden of childhood cancer incidence as experienced by diverse ethnic and socioeconomic groups offers epidemiology an area for insightful innovation in both method and concept.

BIBLIOGRAPHY

Alexander FE, Cartwright RA, McKinney PA, Ricketts TJ. Leukemia incidence, social class and estuaries: an ecological analysis. J Public Health Med 1990; 12(2):109-117.

Arundel SE, Kinnier-Wilson LM. Parental occupations and cancer: a review of the literature. J Epidemiol Community Health 1986; 40:30-36.

Austin H, Cole P. Cigarette smoking and leukemia. J Chronic Disease 1986; 39:417-421.

Breslow NE, Day NE, editors. Statistical methods in cancer research Vol.1. The analysis of case control studies. Lyon, France: International Agency for Research on Cancer; 1980. (IARC Scientific Publication No. 32).

Brownson RC, Novotny TE, Perry MC. Cigarette smoking and adult leukemia. Arch Intern Med 1993; 153:469-475.

Buckley JD, Buckley CM, Ruccione K, Sather HN, Waskerwitz MJ, Woods,WG et al. Epidemiological characteristics of childhood acute lymphocytic leukemia, analysis by phenotype. Leukemia 1994; 8(5):856-863.

Buckley JD, Hobbie WL, Ruccione K, Sather HN, Woods WG, Hammond GD. Maternal smoking during pregnancy and the risk of childhood cancer (letter). Lancet 1986; ii:519-520.

Chilmonczyk BA, Knight GJ, Palomaki GE, Pulkkinen AJ, Williams J, Haddow JE. Environmental tobacco smoke exposure during infancy. Am J Pub Health 1990; 80:1205-1208.

Choi BCK, Noseworthy AL. Classification, direction, and prevention of bias in epidemiologic research. J Occup Med 1992; 34(3):265-271

Choi BCK, Pak AWP. Bias, Overview. In: Armitage P, Colton T, editors. Encyclopedia of biostatistics. Chichester, Sussex, UK: John Wiley and Sons Ltd. 1:331-338.

Cnattingius S, Zack MM, Ekbom A, Gunnarskog J, Kreuger A, Linet, M et al. Prenatal and neonatal risk factors for childhood lymphatic leukemia. J Natl Cancer Inst 1995; 87:908-914.

Court-Brown WM, Doll R, Bradford Hill A. Incidence of leukaemia after exposure to diagnostic radiation in utero. Br Med J 1960; ii: 1539-1544.

Daling JR, Stazyk P, Olshan AF, Weiss NS. Birth weight and the incidence of childhood cancer. J Natl Cancer Inst 1984; 72(5):1039-1041.

Denissenko MF, Pao A, Tang M-S, Pfeifer GP. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. Science 1996; 274:430-432.

Doll R. The epidemiology of childhood leukaemia. J R Statist Soc 1989; 152:341-351.

Draper GJ, Kroll ME, Stiller CA. Childhood cancer. Cancer Surveys 1994; 19/20:493-517.

Evans RG, Barer ML, Marmor TR, editors. Why are some people healthy and others not?: the determinants of health of populations. New York: Aldine de Gruyter; 1994. p 161-88. (Social Institutions and Social Change Series).

Fasal E, Jackson EW, Klauber MR. Birth characteristics and leukemia in childhood cancer. J Natl Cancer Inst 1971; 47:501-509.

Githens JH, Elliot FE, Saunders LH. The relation of socioeconomic factors to incidence of childhood leukemia. Public Health Rep 1965; 80(7):573-579.

Golding J, Paterson M, Kinlen LJ. Factors associated with childhood cancer in a national cohort study. Br J Cancer 1990; 62:304-308.

Graham S, Levin ML, Lilienfeld AM. The socioeconomic distribution of cancer of various sites in Buffalo, N.Y., 1948-1952. Cancer 1960; 13:180-191.

Graham S, Levin ML, Lilienfeld M, Schuman LM, Gibson R, Dowd JE, Hempelmann L. Preconception, intrauterine, and postnatal irradiation as related to leukemia. National Cancer Institute Monograph 1966; 19:347-371.

Greaves M. A natural history for pediatric acute leukemia. Blood 1993; 82 (4):1043-1051.

Hirayama T. Descriptive and analytical epidemiology of childhood malignancy in Japan. In: Kobayashi N, editor. Recent advances in management of children with cancer. Tokyo: The Children's Cancer Association of Japan 1980: p. 27-43.

International Agency for Research on Cancer. Evaluation of the carcinogenic risk of chemicals to humans: tobacco smoking. Lyon, France: World Health Organization; 1986. (IARC Monographs Vol. 38).

Jenkins PL, Phillips TJ, Mulberg EG, Hui SP. Activity patterns of Californians: use of and proximity to indoor pollutant sources. Atmos Environ 1992; 26A:2141-2148.

Ji BT, Shu XO, Linet MS, Zheng W, Wacholder S, Gao YT et al. Paternal cigarette smoking and the risk of childhood cancer among offspring of nonsmoking mothers. J Natl Cancer Inst 1997; 89(3):238-44.

Jordanov JS. Cotinine concentrations in amniotic fluid and urine of smoking, passive smoking and non-smoking pregnant women at term and in the urine of their neonates on 1st day of life. Eur J Pediatr 1990; 149:734-737.

Kaufman J. Progress and pitfalls in the social epidemiology of cancer. Cancer Causes Control 1999; 10: 489-494.

Kaye SA, Robison LL, Smithson A, Gunderson P, King FL, Neglia JP. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. Cancer 1991; 68:1351-1355.

Kinlen LJ, Petridou E. Childhood leukemia and rural population movements: Greece, Italy, and other countries. Cancer Causes Control 1995; 6:445-450

Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull WHO 1987; 65:663-737

Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. Annu Rev Public Health 1997; 18:341-78.

Krishnamurthy S, Dhar M. Cancer and other causes of childhood mortality in Bombay, India. Cancer1991; 68:1848-1853.

Liberatos P, Link BG, Kelsey JL. The measurement of social class in epidemiology. Epidemiol Rev 1988; 10:87-121.

Linet MS, Devesa SS. Descriptive epidemiology of childhood leukemia. Br J Cancer 1991; 63:424-429.

Little, J. Epidemiology of childhood cancer. Lyon, France: International Agency for Research on Cancer; 1999; (IARC Scientific Publication No. 149).

Lovallo WR. Stress and health: biological and psychological interactions. London: Sage Publications; 1997. p. 123-44. (Behavioural Medicine and Health Psychology Series).

Luck W, Nau H. Nicotine and cotinine concentrations in serum and urine of infants exposed via passive smoking or milk from smoking mothers. J Pediatr 1985; 107:816-820.

Malkin D. Cancers of childhood. In: DeVita VT, Jr, Hellman S, Rosenburg SA, editors. Cancer: principles and practice of oncology. 5th ed. New York: Lippincott-Raven; 1997; p. 2083-2091.

Manning MD, Carroll BE. Some epidemiological aspects of leukemia in children. J Natl Cancer Inst 1957; 19:1087-1094.

McBride ML, Gallagher RP, Theriault G, Armstrong BG, Tamaro S, Spinelli, JJ et al. Power-frequency electric and magnetic fields and risk of childhood leukemia in Canada. Am J Epidemiol 1999; 149(9):831-842.

McWhirter WR. The relationship of incidence of childhood lymphoblastic leukemia to social class. Br J Cancer 1982; 46 (4):640-645.

Miller RW. Childhood leukemia and neonatal exposure to lighting in nurseries. Cancer Causes Control 1992; 3:581-582.

Monson RR, MacMahon B. Prenatal X-ray exposure and cancer in children. In: Boice JD, Jr, Fraumeni JF, Jr, editors. Radiation carcinogenesis: epidemiology and biological significance. New York: Raven Press; 1984. p. 97-105.

National Cancer Institute of Canada. Canadian cancer statistics 1999. Toronto, Canada: 1999.

National Cancer Institute. Health effects of exposure to environmental tobacco smoke. National Institutes of Health; 1999; p.40. (Smoking and Tobacco Control Monograph 10).

Neglia JP, Robison LL. Epidemiology of the acute childhood leukemias. Pediatr Clin North Am 1988; 35 (4):675-692.

Neutel IC, Buck C. Effect of smoking during pregnancy on the risk of cancer in children. J Natl Cancer Inst 1971; 47:59-63.

Overpeck MD, Moss AJ. Children's exposure to environmental cigarette smoke before and after birth: health of our nation's children, United States, 1988. National Center for Health Statistics, Hyattsville Maryland: 1991. (Advance data from vital and health statistics No. 202).

Parkin DM, Stiller CA, Draper GJ, Bieber CA. The international incidence of childhood cancer. Int J Cancer 1988; 42: 11-520.

Parkin DM, Kramarova E, Draper GJ, Masuyer E, Michaelis J, Neglia J et al. International incidence of childhood cancer, Vol II. Lyon, France: International Agency for Research on Cancer; 1998. (IARC Scientific Publications No. 144).

Pershagen G, Ericson A, Otterblad-Olausson P. Maternal smoking in pregnancy: does it increase the risk of childhood cancer? Int J Epidemio 1992; 21:1-5.

Pinkel D, Nefzger D. Some epidemiological features of childhood leukemia in the Buffalo, N.Y. area. Cancer 1959; 12:351-358.

Powell JE, Parkes SE, Cameron AH, Mann JR. Is the risk of cancer increased in Asians living in the UK? Arch Dis Child 1994; 71:398-403.

Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin, GR, editors. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, MD: National Cancer Institute, SEER Program; 1999. (NIH Pub. No. 99-4649).

Robison LL, Codd M, Gunderson P, Neglia JP, Smithson WA, King FL. Birth weight as a risk factor for childhood acute lymphoblastic leukemia. Pediatc Hematol Oncol 1987; 4 (1):63-72.

Sacks MS, Seeman I. A statistical study of mortality from leukemia. Blood 1947; 2:1-14.

Sanders BM, White GC, Draper GJ. Occupations of fathers of children dying from neoplasms. J Epidemiol Community Health 1981; 35:245-250.

Savitz DA, Ananth CV. Birth characteristics of childhood cancer cases, controls and their siblings. Pediatr Hematol Oncol 1994; 11:587-599.

Savitz DA, Chen J. Parental occupation and childhood cancer: review of epidemiologic studies. Environ Health Perspect 1990; 88:325-337

Schlesselman, James J. Case control studies: design, conduct, analysis. Oxford: Oxford University Press; 1982.

Schulte-Hobein B, Schwartz-Bickenback D, Abt S, Plum C, Nau H. Cigarette smoke exposure and development of infants throughout the first year of life: influence of passive smoking and nursing on cotinine levels in breast milk and infant's urine. Acta Paediatrica Scandinavica 1992; 81:550-557.

Severson RK, Buckley JD, Woods WG, Benjamin D, Robison LL. Cigarette smoking and alcohol consumption by parents of children with acute myeloid leukemia: an analysis within morphological subgroups – a report from the Children's Cancer Group. Cancer Epidemiol Biomarkers Prev 1993; 2:433-439.

Shaw G, Lavey R, Jackson R, Austin D. Association of childhood leukemia with maternal age, birth order and paternal occupation: a case-control study. Am J Epidemiol 1984; 119:788-795.

Shu XO, Gao YT, Brinton LA, Linet MS, Tu, JT, Zheng W. et al A population-based case-control study of childhood leukemia in Shanghai. Cancer 1988; 62: 635-644.

Shu XO, Ross JA, Pendergrass TW, Reaman GH, Lampkin B, Robison LL. Parental alcohol consumption, cigarette smoking and risk of infant leukemia: a Childrens Cancer Group Study. J Natl Cancer Inst 1996; 88: 24-31.

Smulevich VB, Solionova LG, Belyakova SV. Parental occupation and other factors and cancer risk in children: I. study methodology and non-occupational factors. Int J Cancer 1999; 83:712-717.

Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. Br Med J 1958; 1:1495-1508.

Stark CR, Mantel N. Effects of maternal age and birth order on the risk of mongolism and leukemia. J Natl Cancer Inst 1966; 37:687-698.

Stark CR, Mantel N. Maternal age and birth order effects in childhood leukemia: age of child and type of leukemia. J Natl Cancer Inst 1969; 42(5): 857-66.

Statistics Canada. Standard Occupational Classification 1980. Statistics Canada Standards Division. Ottawa. 1981.

Stiller CA, McKinney PA, Bunch KJ, Bailey CC, Lewis IJ. Childhood cancer and ethnic group in Britain: a United Kingdom Children's Cancer Study Group (UKCCSG) study. Br J Cancer 1991; 64:543-548.

Stjernfeldt M, Berglund K, Lindsten J, Ludvigsson J. Maternal smoking and irradiation during pregnancy as risk factors for child leukemia. Cancer Detect Prev 1992; 16(2):129-135.

Stjernfeldt M, Lindsten J, Berglund K, Ludvigsson J. Maternal smoking during pregnancy and risk of childhood cancer. Lancet 1986; i:1350-1352.

Van Duijn CM, van Steensel-Moll HA, Coebergh JW, van Zanen GE. Risk factors for childhood acute non-lymphocytic leukemia: an association with maternal alcohol consumption during pregnancy. Cancer Epidemiol Biomarkers Prev 1994; 3:457-460.

Walter WA, Gilliam AG. Leukemia mortality: geographic distribution in the United States for 1949-51. J Natl Cancer Inst 1956; 17:475-480.

Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. Am J Epidemiol 1979; 109:273-284.

Wertelecki W, Mantel N. Increased birth weight in leukemia. Pediatr Res 1973; 7 3):132-138.

Woodward A, Grgurinovich N, Ryan P. Breast feeding and smoking hygiene: major influences on cotinine in urine of smokers' infants. J Epidemiol Community Health 1986; 40:309-315.

Zack M, Adami HO, Ericson A. Maternal and perinatal risk factors for childhood leukemia. Cancer Res 1991; 51:3696-3701.

Zenzes MT, Puy LA, Bielecki R, Reed TE. Detection of benzo[a]pyrene diol epoxide-DNA adducts in embryos from smoking couples: evidence for transmission by spermatozoa. Mol Hum Reprod 1999; 5(2):121-131.

APPENDIX I: TABLES 1- 9

Table 1. Participation Rates

Participant Response Status	Case (n)	Case (%)	Control (n)	Control (%)
Potential subjects ascertained	449		675	
Could not find	4		149	
Total eligible respondents	445	100	526	100
Physician refusal	14	3	0	
Family refusal	29	7	116	22
Refusal for health reasons	0	0	7	1
Refusal due to language difficulty	3	<1	4	<1
Total refusals	46	10	127	24
Participating subjects	399	90	399	76

Table 2. Comparison of characteristics of participating cases and controls

Characteristic	Cases (n)	Cases (%)	Controls (n)	Controls (%)
Gender				
Female	196	49	196	49
Male	203	51	203	51
Missing	0		0	
Province				
British Columbia	105	26	105	26
Alberta	59	15	59	15
Saskatchewan	24	6	24	6
Manitoba	25	6	25	6
Quebec	186	47	186	47
Missing	0		0	
Age at dx or reference date				
<18 months	36	9	33	8
18 months to 4 years	190	48	188	47
5-9 years	105	26	113	28
10-14 years	68	17	65	16
Missing	0		0	
Household Income				
<$15,000	45	12	29	7
15-29,999	76	20	56	14
30-44,999	93	24	102	26
>45,000	175	45	208	53
Missing	10		4	
Mother's Age				
< 25 yr.	96	24	64	16
25-29	153	39	136	35
30-34	112	28	134	34
>= 35	35	9	60	15
Missing	3		5	
Father's Age				
< 25 yr.	50	13	32	8
25-29	127	33	105	27
30-34	123	32	122	32
>= 35	89	23	127	33
Missing	10		13	

Table 2. (cont.)

Characteristic	Cases (n)	Cases (%)	Controls (n)	Controls (%)
Mothers Education				
<8 yr	10	3	10	3
8-11 yr	63	16	47	12
High school	132	33	114	29
Tech\Vocational	85	21	80	20
College\University	99	25	122	31
Graduate Studies	10	3	26	7
Missing	0		0	
Fathers Education				
<8 yr	14	4	10	3
8-11 yr	77	20	55	14
High school	91	23	94	24
Tech\Vocational	83	21	78	20
College\University	96	25	120	31
Graduate Studies	30	8	37	9
Missing	8		5	
Mothers Occupational Status				
Low	38	10	26	7
Intermediate	197	50	157	40
High	91	23	137	35
Homemaker	71	18	77	19
Missing	2		2	
Fathers Occupational Status				
Low	185	47	169	43
Intermediate	95	24	78	20
High	112	29	144	37
Homemaker	0	0	0	0
Missing	7		8	
Ethnic Origin				
Caucasian (all 4 grandparents)	290	79	316	85
Multiple origins	62	17	52	14
Asian (all 4 grandparents)	15	4	5	1
Missing	32		26	

Table 2. (cont.)

Characteristic		Cases (n)	Cases (%)	Controls (n)	Controls (%)
Smoking Status					
Mother					
Smoked month before pregnancy	Yes	149	38	120	30
	No	246	62	273	70
	Missing	4		6	
Smoked during pregnancy	Yes	154	39	121	31
	No	241	61	272	69
	Missing	4		6	
Father					
Smoked month before pregnancy	Yes	185	48	151	40
	No	201	42	224	60
	Missing	13		24	
Smoked during pregnancy	Yes	187	48	161	42
	No	201	42	224	58
	Missing	11		14	

Table 3. Risk of childhood leukemia in relation to various SES indicators, adjusted for age and gender of child and province of residence.

SES indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Household Income						
<$15,000	45	29	1.00			
15-29,999	76	56	0.88	0.49-1.57	.65	
30-44,999	93	102	0.59	0.34-1.01	.06	
>45,000	175	208	**0.54**	**0.33-0.90**	**.02**	
						.003
Mothers Education						
<8 yr	10	10	1.00			
8-11 yr	63	47	1.33	0.51-3.48	.56	
High school	132	114	1.15	0.46-2.88	.77	
Tech\Vocational	85	80	1.06	0.42-2.68	.91	
College\University	99	122	0.80	0.32-2.03	.64	
Graduate Studies	10	26	0.38	0.12-1.20	.10	
						.002
Fathers Education						
<8 yr	14	10	1.00			
8-11 yr	77	55	1.74	0.68-4.47	.25	
High school	91	94	1.72	0.95-3.11	.08	
Tech\Vocational	83	78	1.19	0.68-2.09	.54	
College\University	96	120	1.30	0.73-2.31	.37	
Graduate Studies	30	37	0.98	0.56-1.70	.94	
						.014
Mothers Occup Status						
Low	38	26	1.00			
Intermediate	197	157	0.85	0.50-1.47	.57	
High	91	137	**0.45**	**0.26-0.80**	**.006**	
Homemaker	71	77	0.62	0.34-1.32	.13	
Fathers Occup Status						
Low	185	169	1.00			
Intermediate	95	78	1.10	0.76-1.58	.61	
High	112	144	**0.71**	**0.51-0.98**	**.04**	
Homemaker	0	0				
						.05

Table 4. Univariate analysis of mother's behavioural variables as risk factors for childhood leukemia, adjusted for age and gender of child and province of residence.

Behavioral Indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Mother						
Smoked during pregnancy no	241	272	1.00			
yes	154	121	**1.45**	**1.08-1.95**	**.01**	
Missing	4	6				
Month before, cig/day						
None	246	273	1.00			
< 10	29	22	1.48	0.83-2.66	.19	
10-20	57	47	1.36	0.89-2.09	.16	
>20	63	51	1.38	0.91-2.07	.13	.04
Missing	4	6				
Trimester 1, cig/day						
None	277	299	1.00			
< 10	33	27	1.33	0.78-2.27	.30	
10-20	53	33	**1.75**	**1.10-2.78**	**.02**	
>20	32	34	1.02	0.61-1.70	.94	.16
Missing	4	6				
Trimester 2, cig/day						
None	301	312	1.00			
< 10	22	22	1.04	0.57-1.93	.89	
10-20	47	30	**1.63**	**1.00-2.66**	**.05**	
>20	25	29	0.89	0.51-1.57	.70	.41
Missing	4	6				
Trimester 3, cig/day						
None	300	315	1.00			
< 10	23	21	1.15	0.63-2.13	.65	
10-20	47	30	**1.66**	**1.02-2.70**	**.04**	
>20	25	27	0.98	0.55-1.72	.93	.25
Missing	4	6				

Table 4. (cont.)

Behavioral Indicator		Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
During pregnancy, cig/day							
None		241	273	1.00			
< 10		68	54	1.44	0.97-2.15	.07	
10-20		62	38	**1.86**	**1.12-2.90**	**.006**	
>20		24	28	0.98	0.55-1.73	.93	.06
Missing		4	6				
Alcohol dur pregnancy	no	254	267	1.00			
	yes	141	126	1.16	0.87-1.58	.29	
Missing		4	6				
Month before, drinks/wk							
None		259	272	1.00			
1-2		78	54	**1.52**	**1.03-2.24**	**.04**	
>2		58	67	0.90	0.61-1.34	.62	.82
Missing		4	6				
Trimester 1, drinks/wk							
None		336	328	1.00			
1-2		39	38	1.00	0.62-1.60	.99	
>2		20	27	0.72	0.40-1.31	.29	.37
Missing		4	6				
Trimester 2, drinks/wk							
None		354	344	1.00			
1-2		31	32	0.94	0.55-1.57	.80	
>2		10	17	0.57	0.26-1.27	.17	.21
Missing		4	6				
Trimester 3, drinks/wk							
None		359	344	1.00			
1-2		26	32	0.77	0.45-1.33	.35	
>2		10	17	0.56	0.25-1.25	.16	.10
Missing		4	6				

Table 4. (cont.)

Behavioral Indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
During pregnancy, drinks/wk						
None	256	268	1.00			
1-2	118	97	1.27	0.92-1.75	.14	
>2	21	28	0.78	0.43-1.42	.42	.72
Missing	4	6				

Table 5. Univariate analysis of father's behavioural variables as risk factors for childhood leukemia, adjusted for age and gender of child and province of residence.

Behav Indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Father						
Smoked during pregnancy no	201	224	1.00			
yes	187	161	1.30	0.98-1.73	.07	
Missing	11	14				
Prior to pregnancy , cig/day						
None	201	224	1.00			
< 10	23	20	1.29	0.69-2.41	.43	
10-20	53	35	**1.69**	**1.06-2.69**	**.03**	
>20	109	96	1.29	0.92-1.80	.14	.06
Missing	13	24				
Trimester 1, cig/day						
None	201	224	1.00			
< 10	20	16	1.39	0.70-2.76	.34	
10-20	46	32	1.60	0.98-2.61	.06	
>20	103	93	1.25	0.88-1.75	.21	.10
Missing	29	34				
Trimester 2, cig/day						
None	201	224	1.00			
< 10	20	15	1.49	0.74-2.98	.27	
10-20	41	31	1.46	0.88-2.42	.14	
>20	100	90	1.25	0.89-1.77	.20	.12
Missing	37	39				
Trimester 3, cig/day						
None	201	224	1.00			
< 10	20	15	1.49	0.74-2.98	.26	
10-20	41	31	1.46	0.88-2.43	.14	
>20	102	90	1.28	0.91-1.81	.16	.10
Missing	35	39				

Table 5. (cont.)

Behav Indicator		Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
During pregnancy, cig/day							
None		201	224	1.00			
< 10		28	19	1.64	0.89-3.05	.11	
10-20		42	31	1.50	0.91-2.48	.11	
>20		101	90	1.27	0.90-1.79	.18	.11
Missing		27	35				
Alcohol dur pregnancy	no	141	140	1.00			
	yes	247	246	1.00	0.74-1.34	.99	
Missing		11	13				
1 Year prior, drinks/wk							
None		141	140	1.00			
1-3		76	68	1.11	0.74-1.66	.61	
4-7		59	65	.90	0.59-1.38	.63	
8-14		54	56	.96	0.62-1.49	.85	
>14		54	55	.98	0.63-1.52	.92	.74
Missing		13	15				
Parents smoke during preg							
Neither		156	187	1.00			
Father only		83	83	1.21	0.84-1.76	.31	
Mother only		44	37	1.45	0.89-2.37	.14	
Both		104	78	**1.62**	**1.12-2.33**	**.01**	**.007**
Missing		12	14				
Parents alcohol during preg							
Neither		118	122	1.00			
Father only		132	140	0.98	0.69-1.38	.89	
Mother only		22	18	1.25	0.64-2.46	.52	
Both		115	106	1.12	0.78-1.61	.55	.45
Missing		12	13				

Table 6. **Univariate analysis of demographic variables as risk factors for childhood leukemia, adjusted for age and gender of child and province of residence.**

Indicator	Cases (n)	Controls (n)	OR	95% CI	P value	P value (trend)
Mothers Age						
<25 yrs.	96	64	1.00			
25-29	153	136	**2.62**	**1.55-4.44**	**.0003**	
30-34	112	134	**1.96**	**1.21-3.16**	**.006**	
>=35	35	60	1.43	0.88-2.33	.15	**.0001**
Birthweight						
< 2500 g.	23	17	1.45	0.75-2.81	.27	
2500 – 3499	192	206	1.00			
3500 – 3749	88	80	1.18	0.82-1.70	.37	
> 3750	95	94	1.08	0.76-1.54	.65	
Missing	1	2				
Gestational Period						
<=36 weeks	26	23	1.19	0.63-2.22	.59	
37-39 weeks	97	102	1.00			
40-41 weeks	218	222	1.03	0.73-1.45	.84	
>=42 weeks	54	50	1.14	0.71-1.83	.59	
Missing	4	2				
Ethnic origin of child						
Caucasian	290	316	1.00			
Other	77	57	**1.49**	**1.02-2.17**	**.04**	
Caucasian	290	316	1.00			
Other-non Oriental	59	44	1.47	0.96-2.25	.07	
Oriental (1 grandparent)	18	13	1.53	0.73-3.18	.25	
Caucasian	290	316	1.00			
Other-non Oriental	62	52	1.31	0.88-1.96	.18	
Oriental (4 grandparent)	15	5	**3.31**	**1.19-9.23**	**.02**	

Table 7. Risk of childhood leukemia in relation to mother's x-ray exposure, adjusted for age and gender of child and province of residence.

X ray indicator	Cases (n)	Controls (n)	OR	95% CI	P value
Xray 2 yr before preg.					
None	283	290			
Any	83	87	0.98	0.70-1.4	.93
Missing	33	22			
Xray month before preg.					
None	358	373			
Any	4	2	2.06	.38-11.3	.40
Missing	37	24			
Xray during preg					
None	369	365			
Any	20	27	0.74	0.40-1.3	.31
Missing	10	7			
Xray pelvimetry dur preg					
None	385	377			
Any	10	16	0.61	0.27-1.37	.23
Missing	4	6			
Therapeutic Xrays					
2 yr prior to preg					
None	362	373			
Any	0	2			
Missing	37	24			
Month before preg					
None	362	375			
Any	0	0			
Missing	37	24			
During preg					
None	389	391			
Any	0	0			
Missing	10	8			
Pelvimetry dur. preg					
None	395	393			
Any	0	0			
Missing	4	6			

Table 8. **Univariate analysis of fathers usual occupation as a risk factor for childhood leukemia, adjusted for age and gender of child and province of residence.**

Usual Occupation in Service Industry	Cases (n)	Controls (n)	OR	95% CI	P value
Father					
Services	35	24	1.50	0.87-2.58	.14
Food beverage services	17	7	**2.48**	**1.01-6.06**	**.05**
Chefs and Cooks	11	4	2.78	0.88-8.82	.08
Mother					
Services	48	30	**1.69**	**1.04-2.72**	**.03**
Food Beverage Services	20	9	**2.29**	**1.03-5.09**	**.04**
Hairdressers	16	8	2.05	0.87-4.85	.10

Table 9. Summary of Models 1-5: Multivariate analysis using forward/backward stepwise logistic regression adjusted for age group, gender and province.

Variables in each model selected from univariate analysis	OR	95% CI	P value
Model 1: SOCIO-ECONOMIC STATUS			
Mother's Education			
Household Income			
<$15,000	1.00		
15-29,999	0.70	0.37-1.30	.25
30-44,999	**0.47**	**0.26-0.85**	**.01**
>45,000	**0.50**	**0.28-0.87**	**.01**
Mother's SES by Occupation			
Low	1.00		
Intermediate	0.84	0.48-1.48	.55
High	**0.49**	**0.27-0.88**	**.01**
Homemaker	0.58	0.32-1.08	.08
Father's SES by Occupation			
Father's Education			
Model 2: BEHAVIOUR			
Mother cig/day dur preg			
None	1.00		
< 10	1.38	0.92-2.08	.12
10-20	**1.98**	**1.26-3.13**	**.003**
> 20	0.99	0.55-1.79	.97
Father cig/day dur preg			
Mother drinks/week, month before preg			
None	1.00		
1-2	1.48	0.99-2.20	.05
>2	0.85	0.56-1.29	.44

Table 9. (cont.)

Model 3: DEMOGRAPHICS	OR	95% CI	P value
Ethnic origin			
Caucasian	1.00		
Other-non Oriental	1.30	0.86-1.96	.20
Oriental (4 grandparent)	**3.56**	**1.27-9.99**	**.02**
Mother's age			
<25 yrs.	1.00		
25-29	0.73	0.49-1.1	.13
30-34	**0.56**	**0.37-0.86**	**.008**
>=35	**0.40**	**0.23-0.69**	**.001**
Model 4: ENVIRONMENTAL TOBACCO EXPOSURE			
Mother: cig/day dur pregnancy			
None	1.00		
< 10	1.42	0.94-2.13	.10
10-20	**1.99**	**1.26-3.14**	**.003**
> 20	0.99	0.55-1.79	.98
Father: food and bev.serv. 13B			
No			
Yes			
Mother: food and bev.serv 13B			
Father: cig/day prior to pregnancy			

Table 9. (cont.)

Model 5 COMBINATION OF MODELS 1-4	OR	95% CI	P value
Mother's Age			
Ethnic Origin			
Caucasian (all 4 grandparents)	1.00		
Multiple Origins	1.38	0.91-2.09	.13
Asian (all 4 grandparents)	**3.65**	**1.27-10.52**	**.02**
Mother cig/day dur pregnancy			
None	1.00		
< 10	1.45	0.94-2.23	.09
10-20	**1.80**	**1.12-2.90**	**.02**
> 20	0.90	0.47-1.72	.75
Income			
Mother's SES by occ			
Low	1.00		
Intermediate	0.87	0.48-1.54	.62
High	**0.48**	**0.26-0.88**	**.02**
Homemaker	0.64	0.34-1.22	.17
Mother drinks/week, month before preg			
None	1.00		
1-2	**1.77**	**1.17-2.70**	**.007**
> 2	0.84	0.55-1.30	.44