OXYGEN, PHOTOTHERAPY, PERINATAL FACTORS AND RISK OF ACUTE LYMPHOCYTIC LEUKEMIA

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ABSTRACT

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Background: A growing body of evidence suggests that a number of perinatal factors may increase the risk of acute lymphocytic leukemia (ALL), the most common childhood cancer.

Objective: To better understand perinatal factors associated with ALL with particular attention to oxygen supplementation, phototherapy, and fetal growth ratio (FGR).

Materials and Methods: In Phase I of this research, all children (n =1,021) with histologically-confirmed ALL diagnosed in Michigan between 1985 and 2003 were ascertained in the population-based Michigan Cancer Registry. Their records were linked by the Michigan Department of Community Health (MDCH) to their birth certificates. The MDCH randomly selected, from birth certificate files, two surviving (to age one year) children as controls for each case, matched on hospital of birth, gestational age (GA +/- two weeks), sex, month and year of birth. In Phase II, maternal and newborn records of a subset of cases (n=231) and matched controls (n=377) born in 12 large hospitals in Michigan were reviewed. Odds ratio (OR) and 95% confidence interval (CI) were estimated using conditional logistic regression.

Results: In Phase I, 867 ALL cases were successfully matched with 1,416 controls. Mean birth weight (BW) was 3,459 g for cases and 3,399 g for controls (mean difference = 60 g). Significant ORs were obtained for white maternal race (2.4, CI 1.7-3.5; black as reference), white paternal race (2.5, CI 1.6-4.1), maternal age > 18 y (1.6, CI 1.0-2.4), and BW of ≥ 4,000 g (1.47, CI 1.06-2.03). Compared to infants with slow fetal growth (FGR below the 25th percentile), infants with rapid fetal growth (FGR > 75th percentile) had the odds of

1.52 (CI 1.1- 2.1) for developing ALL [OR 1.48 (CI 1.16-1.91) after adjusting for maternal race]. A significant excess risk (OR 2.58, CI 1.11-5.99) was found in high BW babies whose mothers smoked during pregnancy. Based on the data from Phase II, neonatal exposure to X-ray carried an OR of 1.73 (CI 0.99-3.04). Jaundice observed in the first 24 hours after birth was associated with an OR of 1.92 (CI 0.97-3.79). No excess risk of ALL with oxygen exposure in the delivery room was found (OR 0.8, CI 0.56-1.15). However, the OR for oxygen exposure post delivery room was 1.61 (CI 0.93-2.77). After adjustment for potential confounders (maternal age and race, X-ray exposure, early neonatal jaundice, and Apgar score at 5 minutes), this latter OR was reduced to 1.16 (CI 0.46-2.91). Maternal exposure to oxygen in labor was not associated with ALL. An OR of 0.88 (CI 0.44-1.74) was found for infant phototherapy and ALL.

Conclusions: We did not confirm study hypotheses relating either oxygen exposure or phototherapy to ALL. We did confirm the finding that black children in the US are at lower risk of ALL than white children. We also extend the consistent finding of higher BW in ALL, adding the insight that this association is specific to fetal growth in the highest quartile. A condition often associated with oxygen exposure, X-ray exposure, which in these data was mainly chest X-rays for respiratory disease, was associated with a borderline significant 73% excess of ALL. While we expected that phototherapy might be associated with ALL, its treatment target, hyperbilirubinemia, was nearly significantly positively associated with ALL. Two unpredicted associations with ALL were a reduction of risk in mothers < 18 y, and an interaction of smoking and high fetal growth.

I dedicate this dissertation to my mentors and teachers around the world.

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PREFACE

This dissertation provides detailed results of a two-phase study which started in 2007 and completed in 2010. Chapter 1 includes a review of epidemiological features and risk factors of ALL, the most common childhood cancer. Chapter 2 covers a thorough review of the main exposures of interest, oxygen and phototherapy. This chapter sets a multi-faceted background for the discussions included in Chapter 3.

Chapter 3 provides results of the analyses of the data collected from the hospitals (Phase II of the study). Chapter 4 presents results of the analyses of the linked data provided by the MDCH. The final chapter provides a summary of the latest scientific achievements in etiological studies of ALL as well as the directions for future investigations.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

KEY TO ABBREVIATIONS

AL	Acute leukemia
ALL	Acute lymphocytic (or lymphoblastic) leukemia
ALL/L	Acute lymphoblastic leukemia/lymphoma
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
BRIC	Biomedical Research Informatics Core
BW	Birth weight
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CNS	Central nervous system
CPP	Collaborative Perinatal Project
CRIRB	Community Research Institutional Review Board
DB	Data base
DBS	Dried blood spot
DNA	Deoxyribonucleic acid
DS	Down syndrome
ELBW	Extremely low birth weight
EMF	Electromagnetic field
FG	Fetal growth
FGR	Fetal growth ratio
GA	Gestational age

GF	Growth factor
GH	Growth hormone
HBW	High birth weight
HIF	Hypoxia inducible factor
HLA	Human leukocyte antigen
HR	Hazard ratio
HSC	Hematopoietic stem cell
IGF	Insulin-like growth factor
IR	Incidence rate
IRB	Institutional review board
IRR	Incidence rate ratio
LBW	Low birth weight
LIF	Leukemia inhibitory factor
MDCH	Michigan Department of Community Health
MRN	Master record number
MSU	Michigan State University
NBW	Normal birth weight
NCI	National Cancer Institute
NICU	Neonatal intensive care unit
O_2	Oxygen
OFR	Oxygen-free radical
OR	Odds ratio
PaO_2	Partial pressure of oxygen in arterial blood

POBW	Proportion of optimal birth weight
ROS	Reactive oxygen species
RR	Rate ratio, risk ratio
SaO_2	Arterial oxygen saturation
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SES	Socioeconomic status
SIR	Standardized incidence ratio
SpO_2	Saturation of hemoglobin with oxygen
TNF	Tumor necrosis factor
VLBW	Very low birth weight

Chapter 1: EPIDEMIOLOGICAL REVIEW OF ACUTE LYMPHOCYTIC LEUKEMIA

Leukemia, a cancer of the bone marrow and blood, is classified into four groups according to cell type: acute lymphocytic (ALL), chronic lymphocytic (CLL), acute myeloid (AML), and chronic myeloid (CML). Leukemia may present with bone and joint pain, weakness, bleeding, and fever, or may be discovered incidentally through blood test. Leukemia incidence rates (IRs) overall have been stable in males and increasing slightly (0.5% per year) in females since 1992.(1)

Cancer among children is much less common than among adults, yet it is the second leading cause of death among children aged 1-14 in the US.(2) Childhood cancers are rare, representing less than 1% of all new cancer diagnoses. Overall, childhood cancer IRs have been increasing slightly by 0.6% per year since 1975.(1)

Leukemias are the most common cancers affecting children, accounting for, in most populations, between 25% and 35% of malignancies.(3) The most common type of leukemia in children is ALL, accounting for three-fourths of leukemia cases among children and adolescents 0 to 19 years of age.(1) ALL is a biologically heterogeneous disease represented by distinct clinical and biological subtypes.(4) Different systems have been used to classify ALL into subtypes.(5)

1.1 Survival

Considerable progress has occurred for many types of childhood cancers, resulting in decreases in cancer death rates among children since 1975, although the rate of decrease has slowed since the mid-1990s.(6) With contemporary improved risk assessment, chemotherapy, hematopoietic stem cell transplantation and supportive care, approximately 80% of children with newly diagnosed ALL can now be cured.(7, 8)

Staging of the disease and patient risk profile are routinely performed to define ALL subtypes and guide management. Complete remission rates are high, especially amongst children (even 100%).(9) Based on the data from the US (2001-2007), B-cell ALL/L had more favorable survival than T-cell ALL/L among the young; the converse occurred at older ages.(10) Within individual tumor types, biological features may be distinctive in the adolescent age group of 15-19 years. (11)

ALL is the most common malignancy associated with venous thromboembolism (VTE) in children.(12) Second malignancies are a significant concern for survivors of childhood ALL, in particular patients who have been treated with cranial irradiation. Brain tumors, most commonly meningiomas, are among the most common second neoplasms discovered in these patients. Breast cancer can occur in association with meningioma, but is not thought to be a consequence of treatment for childhood ALL.(13) Ongoing study of childhood cancer survivors is needed to establish long-term risks and to evaluate the impact of newer techniques such as conformal radiation therapy or proton-beam therapy.(14)

1.2 Descriptive epidemiology

1.2.1 Time trends

Of concern is the long-term increase in cancer IRs among children,(15) which may be because of larger increases in IRs for the lymphoid leukemias and proportionately smaller increases for other childhood cancers.(16) In Europe, the yearly increase of childhood cancer averages 1.1% for the 1978-1997 period and ranges from 0.6% for the leukemias to 1.8% for soft-tissue sarcomas.(17) In the US, ALL rates increased by an average of 0.8% annually during the period 1973–2006, while those for AML increased by an average of 0.9% annually.(18)

The most distinctive features of the geographical distribution of ALL are (i) a tendency towards higher rates in white North American and European populations than in Asian populations and (ii) substantial variations in incidence across continents and within populations. In developed countries, the age-incidence curve of ALL is characterized by a peak between the ages of 1 and 4 years. (19) For many cancer subtypes the estimated timing of underlying step changes in rate appears to correspond with changes in diagnosis or registration procedures.(20) The interpretation of cancer incidence trends is complicated by short-term random variation, artifactual fluctuations introduced by screening, changes in diagnosis or disease classification, completeness of reporting, and by the multiplicity of factors that may affect risk for specific cancer sites.(21)

1.2.2 Risk factors

Cancers are assumed to be multivariate, multifactorial diseases that occur when a complex and prolonged process involving genetic and environmental factors interact in a multistage sequence.(22) A wide range of familial and genetic syndromes is associated with an increased risk of childhood cancer.(23) There are only few known risk factors of childhood leukemia [male sex, age, white race, exposure to ionizing radiation, and certain congenital diseases such as Down syndrome(24)], which account for only 10% of the childhood leukemia cases.(25) Risk factors for the remaining 90% are unknown.(26) Many environmental factors have been proposed as causative for leukemia but only ionising irradiation and certain chemicals, e.g. benzene and cytotoxics (alkylators and topoisomerase II inhibitors), have been confirmed principally for AML.(27)

1.2.2.1 Age

Almost 90% of leukemia cases are diagnosed in adults 20 years of age and older, in whom the most common types are AML and CLL.(1) According to data from Surveillance, Epidemiology and End Results (SEER) Program, during the 1990s, there was a sharp peak in ALL incidence among 2-3 year olds (> 80 per million) which decreased to a rate of 20 per million for 8-10 year olds. The incidence of ALL among 2-3 year olds is approximately 4-fold greater than that for infants and is nearly 10-fold greater than that for 19 year olds.(28)

1.2.2.2 Sex

The ratio of the ALL IRs for boys and girls is usually between 1.1:1 and 1.3:1(29) According to the US data (2001-2007), most subtypes of AML and ALL/L predominate among males,

from a twice higher incidence of T-cell ALL/L among males than among females [incidence rate ratio (IRR) 2.20] to nearly equal IRs of acute promyelocytic leukemia (APL; IRR 1.08).(10)

1.2.2.3 Race

Latino children have higher incidence of leukemia, specifically ALL, than do non-Latino white children.(30, 31) Based on US data (2001-2007), compared with non-Hispanic whites, Hispanics had significantly higher incidence of B-cell ALL/L (IRR 1.64) and APL (IRR 1.28). Blacks had lower IRs of nearly all acute leukemia (AL) subtypes.(10) During the 1970's, the peak was less pronounced for US blacks than for US whites.(29, 32) A recent five-state pooled analysis showed that, compared with whites, black and mixed white/black children had decreased odds ratios (ORs) for ALL, OR 0.39 (95% CI 0.31-0.49) and OR 0.58 (CI 0.37-0.91), respectively.(33)

1.2.2.4 Socioeconomic factors

Connections of socioeconomic status (SES) measures to childhood leukemia are likely to vary with place and time.(34) A systematic review of the current literature on SES and childhood leukemia shows that (a) the results are heterogeneous, with no clear evidence to support a relation between SES and childhood leukemia; (b) a number of factors, most importantly selection bias, might explain inconsistencies between studies; (c) there is some support for an association between SES at birth and childhood leukemia and (d) if there are any associations, these are weak, limited to the most extreme SES groups.(35)

In a British study, population-mixing measures were used as surrogates for quantity and diversity of infections entering the community.(36) The incidence of ALL at ages 1-4 years tended to be higher in rural wards, to increase with the diversity of origin wards from which in-migrants had moved during the year before the census, and to be lower in the most deprived areas. The association is consistent with the higher incidence of leukemia predicted by Kinlen (37), where population mixing results in below average herd immunity to an infectious agent. The apparent specificity to the young childhood age group suggests that the disease more likely occurs when delayed exposure to infection leads to increased immunological stress, as predicted by Greaves(38).

Many factors are related to deprivation including family size.(39) Smith et al argue that systematic variations with socioeconomic factors reported in some ecological studies reflect differences in case notification – not differences in underlying disease occurrence.(40) Under-diagnosis in poorer communities might have contributed to socioeconomic variation in recorded childhood ALL incidence within Great Britain, and elsewhere.(41) There has been a marked increase in the incidence of ALL among young children in New Zealand since the mid 1960s. Poorer families are at greater risk, and there is no clear support for the hypotheses of an infectious cause from the New Zealand data.(42) A very recent Australian study suggested that etiological factors associated with childhood leukemia and SES might have altered over time.(43)

1.2.2.5 Perinatal exposure

Exposures acting before birth and early in life have long been thought to be important determinants of leukemia, and the list of suspected chemical, physical, and biological agents continues to increase. Unfortunately, the evidence regarding the majority of the suggested exposures is limited and often contradictory.(44) Acute leukemia is a consequence of malignant transformation of a hematopoetic progenitor cell. Epidemiological evidence suggests that exposures or events that occur prenatally or in infancy might play a role in the etiology of pediatric acute leukemia.(45) Hjalgrim et al provide further evidence that the development of t(12;21) B-precursor ALL may be initiated in utero. Review of the current literature moreover indicates that age at leukemia may be inversely correlated with the burden of cells with leukemia clonal markers, i.e. leukemia predisposed cells at birth, and that certain types of childhood ALL develop as a multiple step process involving both pre- and postnatal genetic events.(46)

Indeed, the determination of the critical time window of exposure is a scientific challenge. The evidence for exposures occurring during the preconceptional period that have an association with childhood or adulthood cancers is equivocal. Agents definitely related to cancer in children, and adulthood if exposure occurs in utero, include: maternal exposure to ionizing radiation during pregnancy and childhood leukemia and certain other cancers, and maternal use of diethylstilbestrol during pregnancy and clear-cell adenocarcinoma of the vagina of their daughters.(47) The identification of leukemia-associated translocations in umbilical cord blood samples of healthy newborns, suggest that in the future children may be identified prospectively who have an increased risk of developing leukemia.(48, 49)

For some leukemias [e.g., infant myeloid/lymphoid or mixed-lineage leukemia (MLL) positive ALL] the first event appears adequate to create a malignant clone but for the majority of ALL and AML further genetic changes are required, probably postnatal.(27) The nature of pre- and postnatal events involved in leukemogenesis in children is not well understood. The higher incidence of the most common leukemia subtype in affluent societies suggests a contributory role of socioeconomic factors. An abnormal immune response during delayed exposure to common infections provides a plausible mechanism for malignant progression of preleukemic clones in a subgroup of children.(50)

1.2.2.6 Infection

There is growing evidence supporting a role for infections in the etiology of childhood leukemia.(51) (52) It appears increasingly likely that delayed, dysregulated responses to common infectious agents play a major part in the conversion of pre-leukemic clones into overt precursor B cell ALL.(27) According to the Greaves' hypothesis, ALL in children is caused by a lack of exposure to infections in infancy which leads to failure of modulation in the immune system.(53) The marked childhood peak in resource-rich countries and an increased incidence of the childhood peak in ALL (occurring at ages 2-6 years predominantly with precursor B-cell ALL) is supportive of the concept that reduced early infection may play a role.(54)

The Northern California Childhood Leukemia Study showed that, overall, 3 months before pregnancy, during pregnancy, and while breastfeeding, maternal history of influenza/pneumonia was associated with a statistically significant increased risk of ALL in

the offspring (OR 1.89, 95% CI 1.24-2.89), although the risk was non-significant for common ALL (OR 1.41, CI 0.75-2.63). A similar pattern of increased risk was found for history of sexually transmitted disease.(55) The same study showed, in non-Hispanic white children, daycare attendance measured by child-hours was associated with a significantly reduced risk of ALL.(56)

An ecological analysis of the relationship between sanitation, using Helicobacter pylori (H. pylori) as the marker, and the incidence of childhood ALL in 28 countries found inverse associations between H. pylori prevalence and ALL incidence rates in children. These associations were minor and only significant for ALL incidence rates for all cancer registries. They became non-significant and smaller in magnitude when the population source and/or the GNP per capita were added to the relationship.(57) A very recent Danish study (815 cases) found that risk of ALL was associated neither with hospitalizations for infectious diseases before (IRR 0.92, 95% CI 0.78-1.07) nor at/after 2 years of age (IRR 1.04, CI 0.81-1.32). This also applied to subsets of ALL supposedly initiated prenatally.(58)

1.2.2.7 Birth weight

High birth weight (HBW) has been associated with increased risk of childhood leukemia. Caughey and Michels conducted a fixed effects meta-analysis of 32 studies including 16,501 cases of all types of leukemia (OL), 10,974 cases of ALL, and 1,832 cases of AML. The OR for the association of HBW [birth weight (BW) > 4,000 g] with OL, ALL and AML were 1.35 (95% CI 1.24-1.48), 1.23 (CI 1.15-1.32), and 1.40 (CI 1.11-1.76), respectively, compared with normal birth weight (NBW). Low birth weight (LBW) was not associated with overall

and ALL leukemia, but with AML (OR 1.50; CI 1.05-2.13). Per 1,000 g increase in BW, the OR for OL was 1.18 (CI 1.13-1.23) and ALL 1.18 (CI 1.12-1.23). The combined available evidence from observational studies suggests that high BW is associated with an increased risk of overall leukemia and ALL. For AML, the risk may be elevated at both high and low extremes of BW, suggesting a U-shaped association.(59)

Interestingly, a medical record-based study of leukemia and non-Hodgkin's lymphoma diagnosed before the age of 30 years carried out at three hospitals in the south of England (177 cases, 354 age- and sex-matched controls) showed the preceding siblings of those diagnosed with any form of leukemia were also more likely to weigh > 3,500 g at birth (OR 2.2; 95% CI 1.1-4.4).(60) A multi-country Scandinavian study showed statistically significantly reduced risks of B-precursor ALL with increasing gestational age (GA; OR 0.87 per 2-week increase in GA, 95% CI 0.81-0.94).(61) A very recent pooled analysis of case-control data from Germany, the UK and the US (4,075 ALL cases and 12,065 controls) showed that children with ALL were, on average, heavier than controls at all gestations, the disparity being driven by a deficit of LBW at all gestations and an excess of HBW at 40 weeks. Overall, a 1.2 (95% CI 1.1-1.3) increase in ALL risk per kg increase in BW was observed; the ORs rising from 0.2 (0.1-0.7) at 1,500 g through to 1.2 (0.9-1.6) at 4,500 g; and 0.8 (0.7-0.9) <10th centile through to 1.3 (1.1-1.4) 90th centile.(62)

The biological mechanism behind the HBW-childhood leukemia association may involve insulin-like growth factor I (IGF-I), which is associated with HBW. This growth factor (GF) may act by increasing the absolute number of stem cells available for transformation, stimulating the growth of cells that are already transformed, or a combination of effects.(63)

Malignant tumors have been induced in animals exposed to supraphysiological doses of growth hormone (GH), whereas hypophysectomy appears to protect animals from carcinogen-induced neoplasms. In vitro, proliferation and transformation of normal hemopoetic and leukemic cells occurs with supraphysiological doses of GH, but not with physiological levels. Insulin-like growth factor (IGF), IGF binding proteins (IGFBP) and IGFBP proteases influence the proliferation of cancer cells in vitro; however, GH is probably not involved in this process.(64)

1.2.2.8 Maternal age

Although a Swedish study showed a marginally increased risk of childhood malignancy in the offspring of teenage mothers,(65) another Swedish study showed that older maternal age (≥ 35 years) and lymphatic leukemia were associated with a significantly enhanced risk [standardized incidence ratio (SIR) 2.00; 95% CI 1.16-3.20].(66)

Several studies show an association between high maternal age and ALL.(67) (68) (69) (70) (71) Increased maternal age may serve as an indicator of increased genetic aberrations since elevated maternal age is associated with an increase of DS or other malformation.(72)

1.2.2.9 Genetic factors

Down syndrome (DS) children have an approximately 10- to 20-fold higher risk for developing ALL and AML, as compared with non-DS children.(73) It is unknown why children with DS are at such an increased risk of leukemia.(74)

Associations between Human Leukocyte Antigen (HLA) class II alleles and childhood leukemia have been reported in a number of studies. This could be due to the role of HLA allele-restricted peptide binding and T cell activation, or linkage disequilibrium to a major histocompatibility complex (MHC)-linked leukemia gene in the pathogenesis of childhood leukemia.(75) The cytochrome P450 1A1 (CYP1A1) MspI polymorphism might be a risk factor for ALL, particularly childhood ALL.(76)

To date, there are numerous reports of candidate gene association studies suggesting an involvement of genetic loci in childhood ALL risk.(77) In a Scandinavian study, SIR for familial risk in singleton siblings and twins was 3.2 (95% CI 1.5-5.9) and 162.6 (70.2-320.4), respectively. The data most likely constitute the first demonstration of familial risk for singleton siblings.(78) Most recently, Ma et al sequenced the whole genomes of leukemic cells from two twin pairs with ALL, elucidating the developmental timing of all genetic lesions. Shared, prenatal, coding-region single-nucleotide variants were limited to the putative initiating lesions. By comparing blood and bone marrow samples of the twins in later childhood, the researchers found one genetic mutation identical in both twins - a common leukemia-causing gene called ETV6-RUNX1. The researchers reason that this mutation must have arisen in one of the twins while in the womb. The identical twins had a total of 22 other mutations, but none of these mutations was shared by both twins, and so they must have accumulated after birth as the disease progressed. All other nonsynonymous single-nucleotide variants were distinct between tumors and, therefore, secondary and postnatal.(79)

1.2.2.10 Smoking

Although tobacco smoke is an established risk factor for AML, the studies of association between parental smoking and childhood leukemia have produced inconsistent results.(80) The majority of the studies on maternal smoking and childhood leukemia did not find a significant positive association and some even reported an inverse association.(81) In contrast to studies of maternal smoking, studies of paternal smoking and childhood leukemia reported more positive associations but only by less than half of the studies.(82) A very recent study suggests that heavier paternal smoking around the time of conception is a risk factor for childhood ALL.(83)

1.2.2.11 Chemical exposure

Chronic exposure to high concentrations of benzene is an established cause of AML in occupationally exposed workers.(84) A Mexican study shows that children whose fathers have been exposed to a high level of the carcinogenic agents listed by the IARC seem to have a greater risk of developing acute leukemia.(85) Overall, results of epidemiological studies evaluating outdoor sources of pollution, indoor contaminants and chemicals from drinking water are mostly negative.(86)

1.2.2.12 Pesticide

Residential pesticide exposure may be a contributing risk factor for childhood leukemia but available data are too scarce for causality ascertainment.(87) A recent meta-analysis showed that childhood leukemia was associated with prenatal maternal occupational pesticide exposure (in analyses of all studies combined and in several subgroups). Associations with

paternal occupational pesticide exposure were weaker and less consistent. Research needs include improved pesticide exposure indices, continued follow-up of existing cohorts, genetic susceptibility assessment, and basic research on childhood leukemia initiation and progression.(88)

The Brazilian Collaborative Study Group of Infant Acute Leukemia found that mothers exposed to dipyrone, pesticides and hormones had an increased chance of giving birth to babies with infant acute leukemia [OR 1.48 (95%CI 1.05-2.07)], [OR 2.27 (CI 1.56-3.31)] and [OR 9.08 (CI 2.95-27.96)], respectively.(89) In an Australian study, paternal occupational exposure to pesticides was not found to be associated with an increased risk of ALL in the offspring.(90) Further work is needed to confirm previous findings based on self-report, to examine potential exposure-response relationships, and to assess specific pesticides and toxicologically related subgroups of pesticides in more detail.(91)

1.2.2.13 Ionizing radiation

There is some evidence of an association between environmental radon exposure and elevated childhood leukemia incidence. (92, 93) A very recent British study found that there was 12% excess relative risk (ERR) (95% CI 3- 22%; two-sided P= 0.01) of childhood leukemia per millisievert of cumulative red bone marrow dose from gamma radiation.(94) Multi-site studies around nuclear installations do not indicate an increased risk of childhood leukemia globally.(95)

Compared to the effects of in-utero radiation exposure on childhood cancer, the effects of postnatal diagnostic exposure have been much less studied.(96) (97) Overall, there is very little evidence that exposure to post-natal diagnostic exposure increases childhood cancer risk.(98) More specifically, there is little evidence linking childhood leukemia with lifetime exposure to ionizing radiation.(99) Little concluded that, in most studies of leukemia, there was no association with all types of postnatal exposure to diagnostic and therapeutic ionizing radiation combined.(100)

According to a systematic review, no association of leukemia with prenatal exposures to diagnostic X-rays was observed in 9 case-control studies. Heterogeneous results were found for postnatal exposures and leukemia in four studies.(101) Bailey et al found an increased risk of ALL in the offspring if the father had more than one abdominal X-ray before conception or had ever had an intravenous pyelogram.(102)

In fact, ionizing radiation from X-rays as well as polymorphisms in DNA repair genes(103) are plausible risk factors for childhood leukemia. Infante-Rivard et al conducted a case-control study of childhood ALL measuring reported postnatal X-rays in 701 cases aged 0-14 years and in as many population-based controls matched on age and sex. There was an increase in risk of leukemia with number of X-rays: the adjusted OR for two or more X-rays vs. none was 1.48 (95% CI 1.11-1.97). That risk was slightly higher among girls (OR 1.67). A polymorphism in the APE gene (ex 5) involved in the base excision repair system was suggestive of an increased risk among boys and a reduced risk among girls. HMLH1 (ex 8), a mismatch repair gene, was associated with reduction of risk among girls.(104)

1.2.2.14 Non-ionizing radiation

An association may exist between exposure to low frequency magnetic fields (LF-EMF) and ALL in children,(105) but this association is weak, without consistency in the findings.(106) There is virtually no supportive data from experimental research and, so far, no proposed explanation has reached a level beyond speculation.(107)

Epidemiological evidence showing a consistent association between the risk of childhood leukemia and exposure to power frequency magnetic fields has been accumulating.(108) Three pooled analyses of case-control studies showed a 1.4- to 1.7-fold increased childhood leukemia risk for extremely low-frequency electromagnetic fields (ELF-EMF) exposure levels above 0.3 muT. (109) In reviewing the epidemiological literature on ELF-EMF exposure and childhood leukemia, Mezei et al found evidence both for and against the existence of selection bias. (110) Further studies on the relation between childhood leukemia and EMFs would be worthwhile if they focus on heavily exposed groups and attempt to minimize possible selection bias.(111)

1.2.2.15 Atopy

Atopic disease is hypothesized to be protective against several malignancies, including childhood/adolescent leukemia.(112) Linabery et al reported a summary of 10 case-control studies: ORs for atopy/allergies were 1.42 (95% CI 0.60-3.35) for 3 studies of leukemia overall, 0.69 (CI 0.54-0.89) for 6 studies of ALL, and 0.87 (CI 0.62-1.22) for 2 studies of AML, with high levels of heterogeneity detected for leukemia overall and ALL. Inverse associations were observed for ALL and asthma (OR 0.79, CI 0.61-1.02), eczema (OR 0.74,

CI 0.58-0.96), and hay fever (OR 0.55, CI 0.46-0.66) examined separately. Odds ratios (ORs) for ALL differed by study design, exposure data source, and latency period, indicating that these factors affect study results.(113)

A very recent Greek study (292 cases) found that self-reported-allergic history overall (OR 0.49, 95% CI 0.34-0.72) and practically each one of its main components (respiratory, food, any other clinical allergy) were strongly and inversely associated with ALL. Likewise, the serum IgE inverse association was of the same magnitude (OR 0.43, CI 0.22-0.84) mainly contributed by food IgE (OR 0.39, CI 0.18-0.83).(114) The association between allergies and childhood leukemia may represent some shared underlying immune mechanisms that have been explained in the context of the *hygiene hypothesis*, which has been thought to play an important role in the development of both allergies and childhood leukemia.(115)

A recent Taiwanese study (846 cases, 3,374 controls) suggests that the pathogenesis of childhood ALL and allergy share a common biologic mechanism. This study showed an increased risk of ALL with having an allergy less than 1 year before the case's ALL diagnosis (OR 1.7, 95% CI 1.5, 2.0), more than 1 year before the case's diagnosis (OR 1.3, CI 1.1, 1.5), and before the age of 1 year (OR 1.4, CI 1.1, 1.7).(116) Having any infection before 1 year of age was associated with an increased risk for childhood ALL (OR 3.2, CI 2.2-4.7), with a stronger risk associated with more episodes of infections.(117)

1.2.2.16 Diet

Diet has been linked with leukemia.(118) Increased intake of fruits and vegetables has been associated with decreased leukemia risk.(119) Lack of maternal folate supplementation has been associated with increased childhood leukemia risk, possibly by causing DNA hypomethylation and increased DNA strand breaks. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms modify this risk. (63) Pereira et al found that common genetic C677T polymorphism in the MTHFR contributes to the risk of adult ALL, but not to the childhood ALL susceptibility.(120) Further research into the interaction of folate intake and genotype in causing ALL and other cancers is needed.(121-123)

Consumption of milk and dairy products in the first year of life may protect against childhood leukemia possibly through vitamin D actions.(124) The associations with childhood leukemia and mother's consumption of coffee are ambiguous, with some suggestion of risk at high levels of daily consumption.(125) Inconsistencies in the results and the low risks reported do not suggest an association between childhood cancer and parental consumption of alcohol. (126) The Northern California Childhood Leukemia Study showed that maternal use of iron supplements was indicative of decreased ALL risk (OR 0.67, 95% CI 0.47-0.94).(55) Although much has been documented with regard to diet, smoking, alcohol consumption and recreational and prescription drug use during pregnancy, there is no consistent evidence to support a link with any of these factors and childhood leukemia.(127)

1.3 Discussion

Etiological investigation of childhood leukemia require classification of leukemia at a molecular scale, a comprehensive understanding of genetic risk factors, and an appraisal of infectious exposures and individuals' immune responses.(128) Future epidemiological studies need to assess gene-environment interactions and use improved exposure assessments, including separate parental interviews, specific exposure questions, and semi-quantitative exposure measures that can be used to confirm information obtained through questionnaires.(129)

Current international collaborations, for example in the Childhood Leukemia International Consortium (CLIC), represent an important step forward.(42) Partnerships between a well-established institution or study group and a pediatric cancer unit in a developing country has proved to be the most successful strategy to date.(130, 131)

Chapter 2: EPIDEMIOLOGICAL REVIEW OF NEONATAL OXYGEN THERAPY, PHOTOTHERAPY AND RISK OF ACUTE LYMPHOCYTIC LEUKEMIA

Unlike most other cancers, ALL has a distinctive age distribution characterized by a rapid increase in incidence after birth, a sharp rise between 2 and 5 years of age, and a decline to a steady low incidence for the rest of childhood.(132) The distinct peak of childhood ALL at ages three to four seen in virtually all populations,(29) has suggested that a leukemogenic event may occur during the fetal or perinatal period.(49, 133) Powerful evidence for this proposition comes from the work of Taub et al, who have detected leukemic clones on newborn genetic screening cards of Michigan children later diagnosed with leukemia.(48) Chimeric fusion genes derived by chromosome translocation provide stable, sensitive and clone-specific markers for tracking the origins of leukemic cells and the natural history of disease.(134)

Pregnancy exposures can contribute to human cancer risk, as illustrated most clearly by the finding, in women exposed prenatally to diethylstilbestrol (DES), of a very large excess of clear-cell adenocarcinoma of the vagina.(135) Another suggestion of prenatal influences derives from the consistent finding that high HBW is linked to ALL.(59, 61)

For reasons to be explained below, two additional perinatal factors, oxygen exposure and phototherapy, might also be risk factors for ALL. In addition, both of these commonly used perinatal interventions are under medical control, and may well be overused in current perinatal practice, opening a door to prevention should causality be established.

2.1 Oxygen- biological rationale for a role in leukemogenesis

Oxygen saturation is < 60% in the fetus, a level that would be considered pathological if experienced later in life.(136) While the healthy newborn normally experiences a rise in blood and tissue levels of oxygen upon exposure to room air, in one study median oxygen saturation was just 63% (interquartile range of 53%-68%) in healthy infants at 1 minute of age, and rose gradually to 90% (79%-91%).(137) The process of transitioning to a normal postnatal oxygen saturation requires at least 5 minutes in healthy newborns breathing room air.(138)

A prospective comparison of partial pressure of oxygen in arterial blood (PaO_2) and pulse oxygen saturation values (SpO_2) in 7 NICUs at sea level in two countries showed SpO_2 values of > 93% are frequently associated with PaO_2 values of > 80 mmHg, which may be of risk for some newborns receiving supplemental oxygen.(139) When providing supplemental oxygen, monitoring with modern SpO_2 technology and avoidance of SpO_2 values of 95-100% are less frequently associated with hyperoxemia.(140)

Oxygen supplementation in newborns produces persistence of reactive oxygen species (ROS), detectable for as long as 30 days after even brief exposures.(141) In a trial comparing 100% oxygen to room air for immediate newborn resuscitation only, the reduced-to-oxidized glutathione ratio was significantly lower in the pure oxygen group, revealing protracted oxidative stress, and the activities of superoxide dismutase and catalase in erythrocytes were 69% and 78% higher in the pure oxygen group at 28 days of age.(137)

Animal studies have provided some evidence in favor of oxygen toxicity. Solberg et al studied the dose-response relationship between inspiratory fraction of oxygen used for resuscitation and urinary markers of oxidative damage to DNA and amino acids in newborn piglets. They found that hypoxia and subsequent resuscitation for 15 minutes with graded inspiratory fractions of oxygen resulted in increased oxidative stress and a dose-dependent oxidation of DNA and phenylalanine.(142)

In 1956, Warburg proposed that the origin of cancer cells was closely linked to a permanent respiratory defect that bypassed the Pasteur effect (i.e., the inhibition of anaerobic fermentation by oxygen).(143) Samudio et al show that under normoxic conditions exposure of leukemia cells to bone marrow-derived mesenchymal stromal cells (MSC) promotes accumulation of lactate in the culture medium and reduces mitochondrial membrane potential (DeltaPsiM) in both cell types. Their data suggest that microenvironment activation of highly conserved mammalian uncoupling proteins may facilitate the Warburg effect in the absence of permanent respiratory impairment.(144)

Oxygen has minimal effects on undifferentiated cell growth and phenotype, but may exert more substantial effects under differentiating conditions.(145) Oxidative stress may contribute to newborn tissue injury through mechanisms similar to those produced by inflammation,(146) and may also participate in the carcinogenic process. The complex series of cellular and molecular changes in cancer development may include endogenous damage arising from oxygen-free radicals (OFRs), intermediates of oxygen reduction that attack both DNA bases and the deoxyribosyl backbone of DNA. Improvements in analytical techniques in recent decades have permitted the identification and quantification of adducts of OFRs

with DNA. The most extensively studied lesion is 8-hydroxydeoxyguanine (8-OH-dG), which causes mutations by producing GC→TA transversions. But OFRs can attack other cellular components such as lipids, leaving behind reactive species that can also couple to DNA bases. Reactive oxygen species (ROS) can also act as secondary messengers in intracellular signaling cascades, which induce and maintain the oncogenic phenotype of cancer cells.(147) These observations have led to the widely held view that OFRs are an important class of carcinogens,(148) and that intervention with antioxidants may be an important preventive modality in cancer.(149) Antioxidants prevent the stem cell factor (SCF) effect on glucose transport, confirming the involvement of H_2O_2 in the pathway leading to glucose-transport activation and suggesting a potential role for ROS in leukemia proliferation.(150)

Increased intracellular ROS levels, such as those that result from oncogenic transformation in hematopoietic malignancies, regulate the ability of Nucleostemin (NS), a nucleolar-nucleoplasmic shuttle protein that regulates cell proliferation, to oligomerize, prevent its degradation, and may alter its ability to regulate cell proliferation.(151) An imbalance between oxidants and antioxidants in the plasma of B-chronic lymphocytic leukemia (B-CLL) patients has also been demonstrated. (152) The lower antioxidant status in plasma with ALL children is probably associated with increased ROS.(153)

Sharif et al demonstrated that red wine polyphenolic extract induces apoptosis in human lymphoblastic leukemia cells (Jurkat cells) by a redox-sensitive mechanism involving the intracellular formation of superoxide anions and consequently the up-regulation of p73 and down-regulation of UHRF1.(154) Silva et al showed the existence of a critical crosstalk

between phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway and ROS that is essential for Interleukin-7 (IL-7)-mediated T-cell ALL cell survival, and that may constitute a novel target for therapeutic intervention.(155)

The high sensitivity of hematopoietic cells, especially stem cells, to radiation and to pro-oxidative and other leukemogenic agents could also be attributable to the low number of active mitochondria and the consequently slow utilization of oxygen entering the cell. This results in an increased intracellular partial pressure of O_2 (pO_2) and increased levels of reactive oxygen (ROS) and nitrogen (RNS) species, and a Delta(PO - AO) imbalance between the pro-oxidative (PO) and antioxidative (AO) constituents.(156)

Ray et al reported on the expression and function of two Bcl-2 family members in normal placental development, namely the pro-apoptotic Mtd/Bok, and its anti-apoptotic partner Mcl-1, and found that their expression was upregulated by low oxygen, a key mediator of trophoblast cell proliferation in early placentation. Interestingly, the expression of the Mtd/Mcl-1 system is altered in preeclampsia, a placental pathology associated with a status of oxidative stress and typically characterized by an immature proliferative trophoblast phenotype and excessive trophoblast cell death.(157)

Further investigations on the molecular mechanisms of ROS regulation and the manipulation of excess ROS levels could lead to the development of novel therapeutics for hematopoietic diseases, regenerative medicine, and the prevention of leukemia.(158) A better understanding of the developmental effects of ROS may provide insights for risk

assessment and the reduction of adverse postnatal consequences.(159) The widespread use of oxygen supplementation in newborns, the persistence of ROS in newborn blood for at least a month, the known physiological susceptibility of newborns to oxygen toxicity, and the strong suggestion that ROS are carcinogenic, provide a solid biological substrate for the epidemiological observations linking oxygen exposure in newborns to childhood cancer, and especially leukemia.

2.2 Oxygen- epidemiological evidence for a role in leukemogenesis

Five studies have examined childhood leukemia in relation to exposure to oxygen in the newborn period (Table 2-1). Four Swedish case-control studies, some of which did not clearly distinguish leukemia subtypes, have found significant ORs of 2-3 for the association of childhood leukemia with exposure to oxygen.

Table 2-1 Childhood leukemia/cancer and neonatal oxygen exposure

Principal Author, Publication Year	Population	Cancer Type	Study Design	N Cases	N Controls	Main Exposure	OR
Zack, 1991	Sweden	ALL, AML	Matched case-control	411	2,055	Supplemental oxygen ICD-8 codes 93.32 and 93.70)	**2.6** (a)
Cnattingius, 1995	Sweden	AML CML, type unspecified	Matched case-control	98	490	Supplemental oxygen	2.3 (b)
Cnattingius, 1995	Sweden	ALL, CLL, type unspecified	Matched case-control	613	3,065	Supplemental oxygen	**2.3**
Naumburg, 2002	Sweden	ALL, CLL, type unspecified	Matched case-control	578 Excluding DS	578	100% oxygen by face mask postpartum (Ref: No oxygen by mask) 100% oxygen > 3 minutes (Ref: No oxygen by mask)	**2.6** **3.5**

Table 2-1 (cont'd)

Spector, 2005	USA	All childhood cancers	Historical Cohort (CPP Cohort)	48 16 ALL or AML	54,795 live births	Open/positive-pressure oxygen <2 minutes (Ref: No oxygen exposure)	0.7 (c)
						Open/positive-pressure oxygen > 3 minutes, all children	**2.9** (c)
						Open/positive-pressure oxygen > 3 minutes, children > 1 year	2.0 (c)

(a) Significant ORs bolded
(b) 1.7 if DS cases excluded (84 cases and 420 controls)
(c) Hazard ratio (HR)

The study published by Zack et al in 1991,(160) as stated by Cnattingius et al in1995,(161) was the first to link use of supplementary oxygen to increased risk of childhood lymphatic leukemia. Zack et al describe an exploratory population-based study of maternal and perinatal risk factors for childhood leukemia in Sweden. Mothers of children with leukemia were more likely to have been exposed to nitrous oxide anesthesia during delivery than mothers of controls (OR 1.3, 95% CI 1.0-1.6). Children with leukemia were more likely than controls to have DS (OR 32.5, CI 7.3-144.0) or cleft lip or cleft palate (OR 5.0, CI 1.0-24.8); to have had a diagnosis associated with difficult labor but unspecified complications (OR 4.5, CI 1.1-18.2) or with other conditions of the fetus or newborn (OR 1.5, CI 1.1-2.1), specifically, uncomplicated physiological jaundice (OR 1.9, CI 1.2-2.9); or to have received supplemental oxygen (OR 2.6, CI 1.3-4.9). Cnattingius et al showed that risk of ALL, across all childhood age groups, increased with use of supplementary oxygen (OR 2.3; 95% CI 1.5-3.6).(161) Notably, the risk was stronger than that found for postpartum asphyxia (OR 1.8; 95% CI 1.2-2.6), which is a major risk factor for oxygen administration.

The first study primarily focused on assessing the association between supplementary oxygen and leukemia was published by Naumburg et al (including Cnattingius) in 2002.(162) In fact, this study is considered the most recent case-control study on this topic. Naumburg' study showed that resuscitation with 100% oxygen with a face mask and bag immediately postpartum was associated with a significantly increased risk of ALL (OR 2.6, 95% Cl 1.2-6.8). The risk increased further if ventilation lasted for 3 minutes or more (OR 3.5, CI 1.2-10.8). Low Apgar scores at 1 and 5 minutes were associated with an increased risk of ALL in this study, but not significantly so.

The strengths of Naumburg's study are the population-based design, the large number of cases, the small amount of missing information and the small number of excluded cases. Only 12% of the cases and controls had to be excluded from the original study base because the medical records of the case or control were not found. The loss of subjects was non-differential with regard to exposure to oxygen. The medical records used at antenatal and delivery centers in Sweden were standardized and the records were retrieved in a uniform way. Adjustments were made for potential confounders (such as mother's age, parity and maternal smoking habits), and children with DS, an accepted risk factor for lymphatic leukemia, were excluded.

In a large cohort study in the US, based on the data from the national Collaborative Perinatal Project (CPP), hazard ratio (HR) for all childhood cancers was 2.9 (95% CI 1.5 to 5.7) with exposure to 3 or more minutes of oxygen.(163) Exposure for 2 minutes or less did not raise the risk. In this study too, markers of birth asphyxia were found more commonly in children who later developed childhood cancer, but as in the other two studies, the effect was not as strong as oxygen exposure.

Spector's study did not have sufficient power to assess the effect of neonatal oxygen therapy on ALL alone. Low Apgar score at 1 minute (but oddly, not at 5 minutes) was also associated with cancer risk, but less convincingly than oxygen. In his editorial, Paneth comments: "…*on the grounds of both biologic plausibility and strength of association, oxygen seems a more likely determinant of cancer than does birth depression*". He also noted that if this relationship were truly causal, one in 7 childhood cancers would be prevented by avoidance of use of supplemental oxygen in neonates.(164)

The widespread practice of using pure oxygen immediately after birth to resuscitate depressed newborns may thus easily overshoot physiological norms, and has become an increasingly controversial therapy in newborn medicine. A randomized trial comparing room air to 100% oxygen showed that asphyxiated term infants resuscitated with pure oxygen take longer to produce their first cry than do controls treated with room air (1.7 ± 0.5 vs.1.2 ± 0.6 minutes), and need longer to achieve a sustained respiratory pattern when ventilated (7.5 ± 1.8 vs. 4.6 ± 0.7 minutes).(165)

Higher and more persistent levels of biochemical markers of cardiac and renal damage in asphyxiated infants have also been found in asphyxiated infants treated with pure oxygen compared to room air recipients.(166) Indeed, a systematic review of five trials of this topic found evidence of higher mortality in infants resuscitated with 100% oxygen.(167) It should be noted, however, that in the judgment of a Cochrane review, only two of the trials were randomized and blinded, while the other three were quasi-randomized and not blinded.(168)

Meta-analyses of the studies on term infants receiving resuscitation showed a decrease in mortality with the group for whom resuscitation was initiated with air.(169) (170) Maltepe and Saugstad present evidence describing the role of physiologic hypoxia during development and the adverse consequences of hyperoxia in term as well as preterm infants.(171) A meta-analysis by Saugstad et al showed that the risk of neonatal mortality was reduced in the 21% oxygen group compared to the 100% oxygen group both in the analysis of all studies (typical RR 0.69, 95% CI 0.54, 0.88) and in the analysis of strictly randomized studies (typical RR 0.32, CI 0.12, 0.84). A trend toward decreased risk of

hypoxic ischemic encephalopathy stages 2 and 3 was noted with resuscitation in 21% oxygen in the analysis of all studies (typical RR 0.88, CI 0.72, 1.08).(172)

Saugstad et al characterized the development of clinically relevant variables the first minutes after birth and identified early prognostic markers in newborn infants requiring resuscitation. Heart rate and Apgar scores increased quickly even in the most depressed infants but were significantly lower in those having a poor outcome. The arterial oxygen saturation values increased as quickly in room air as in 100% oxygen resuscitated infants.(173) Hellstrom-Westas et al evaluated data from four Swedish perinatal level III centers during the period 1998-2003. They concluded that severely depressed term infants born in hospitals initiating resuscitation with 40% oxygen had earlier Apgar score recovery than did infants born in hospitals using a 100% oxygen strategy.(174)

In recent years it has become clear that even a brief exposure to high oxygen concentration at birth and an oxygen saturation (SaO_2) > 93-95% in extremely low birth weight (ELBW) infants is more toxic than previously believed. Six studies of ELBW infants have shown that retinopathy of prematurity and chronic lung disease are significantly reduced if SaO_2 is kept < 93-95% compared with higher saturations. Avoidance of fluctuations in SaO_2 also seems to be important.(175) The International Liaison Committee on Resuscitation recommended beginning with air rather than 100% oxygen in term infants receiving resuscitation at birth with positive-pressure ventilation. Because many preterm babies of < 32 weeks of gestation will not reach target saturations in air, blended oxygen and air may be given judiciously and

ideally guided by pulse oximetry. If a blend of oxygen and air is not available, resuscitation should be initiated with air.(176)

Laboring women are also commonly treated with 100% oxygen, but the subject of maternal oxygen supplementation has so far not been investigated for its relationship to offspring childhood cancer. Maternal oxygen supplementation improves the transport of oxygen to fetus but does not appear to have dramatic effects on fetal oxygen saturation levels.(177) Khaw et al showed that breathing high inspired oxygen fraction (FiO_2) modestly increased fetal oxygenation but caused a concomitant increase in OFR activity in both mother and fetus.(178)

2.3 Phototherapy- biological rationale for a role in leukemogenesis

As early as 1937, Najib-Farah demonstrated a protective effect of bilirubin in bacterial infections.(179) The pathophysiology of neonatal jaundice is not fully understood but a link with estrogens that have growth-promoting potential has been suggested.(180, 181) Enzymatic conversion of biliverdin to bilirubin by the enzyme biliverdin reductase results in protection from oxidative stress.(182) The bilirubin-biliverdin interconversion cycle amplifies the antioxidant actions of bilrubin.(183) While very low birth weight (VLBW) infants are more susceptible than term infants to CNS toxicity from indirect hyperbilirubinemia, bilirubin may play a particularly beneficial role as an antioxidant and enzyme inducer in these vulnerable infants.(184) The carcinogenicity of phototherapy may thus arise from either or both of two pathways. In the process of breaking down bilirubin,

phototherapy may increase ROS, or phototherapy may release carcinogenic substances as a result of bilirubin breakdown.

Ben-Sasson and Davis offer the hypothesis that exposure to photosensitizing lighting immediately after birth may be a contributing cause of ALL because fluorescent lamps and other light sources with strong illumination – around 400 nm – are protoporphyrin-activating. Activation of protoporphyrin produces superoxides and free radicals that can induce breaks in DNA.(185) Untoward effects of phototherapy on DNA have been demonstrated in vitro.(186) Lipinski et al detected induction of oxidative DNA lesions in cultured cells irradiated with fluorescent light.(187) However, specific chemical nature of DNA damage induced by fluorescent light has not been well determined. One theory proposes that phototherapy treatment of neonatal jaundice causes free radicals to circulate in the newborn, resulting in transformation of lymphoblasts by altering DNA.(185) Although results of the study by Podvin et al (71) supports this hypothesis, it has been challenged by studies that have found no evidence of increased risk of leukemia associated with phototherapy use.(188) (161) (189) (60) (190)

Biological evidence hints at a possible interaction between phototherapy and ROS (possibly due to oxygen supplementation). Scharff et al demonstrated the ability of photo excited supramolecular composites containing fullerenes C60 immobilized at nanosilica particles to generate ROS in cells of two types (rat thymocytes, and transformed cells of ascite Erlich carcinoma, EAC, and leucosis L1210).(191) Haruna et al demonstrated that hydroxyl radicals generated selectively by photolysis of a photo-Fenton reagent, N,N'-bis(2-hydroperoxy-2-methoxyethyl)-1,4,5,8-naphthaldiimide (NP-III), induce apoptosis in HL-60

(human promyelocytic leukemia) cells involving the activation of caspase-3.(192) Under 365-nm light irradiation, a novel isoquino[4,5-bc]acridine derivative damaged plasmid DNA pBR322 at <2 microM and cleaved DNA from form I to 100% form II by 50 microM. The mechanism studies revealed that this agent damaged DNA by electron transfer mechanism and singlet oxygen species.(193)

2.4 Phototherapy- epidemiological evidence for a role in leukemogenesis

Approximately two thirds of the more than 4 million neonates born annually in the US become clinically jaundiced.(194) Phototherapy is a simple, easy-to-use tool that reduces serum indirect hyperbilirubinemia by breaking down bilirubin into other molecules thereby preventing the kernicteric brain damage that can occur in neonates with severe hyperbilirubinemia. Approximately 9% of newborns in the US receive phototherapy,(195, 196) even though the vast majority do not have jaundice severe enough to lead to significant harm if left untreated.

Physiologic jaundice in premature neonates is more severe than in full-term neonates, with mean peak total serum bilirubin (TSB) concentrations reaching 10 to 12 mg/dl (171 to 205 μmol/L) by the 5th day of life.(197) Thus, premature babies, including babies born mildly prematurely and not treated in NICUs, are especially likely to receive phototherapy. Despite its widespread use, phototherapy is not well standardized in practice in the US, and a variety of devices delivering phototherapy with varying efficacies are produced and used.

Bilirubin absorbs light maximally in the blue range (340 to 540 nm); daylight and cool white lamps which have a spectral emission of 370 to 430 nm may be less effective than blue lamps which have a narrower spectral range with a peak between 420 and 480 nm.(198) Many light sources used in phototherapy produce significant quantities of ultraviolet (UV) light.(199) Intensive neonatal phototherapy is a strong risk factor for nevus (a cutaneous melanoma risk factor) development in childhood.(200)

Table 2-2 Childhood leukemia/cancer and phototherapy

Principal Author, Publication Year	Population	Cancer Type	Study Design	N Cases	N Controls	Main Exposure	OR
Van Steensel-Moll, 1992	The Netherlands	ALL	Matched case-control	238	196	Phototherapy (blue light 420-470 nm)	3.6
Cnattingius, 1995	Sweden	AML CML, type un-specified	Matched case-control	98	490	Phototherapy	7.5 (a)
Olsen, 1996	Denmark	All childhood cancers	Cohort	87 (28 ALL)	55,120 Mature neonates with hyper-Bilirubinemia	Phototherapy (prolonged irradiation with light at wavelengths of 420-470 nm), all childhood cancers ALL	1.0 (b) 1.1 (b)
Roman, 1997	England	ALL	Matched case-control	113	100	Phototherapy	0.6

(a) 4.3 if DS cases excluded
(b) Standardized incidence ratio

Three studies have examined ALL following phototherapy in the newborn period (Table 2-2). A Dutch register-based matched case-control study reported a higher frequency of phototherapy among 519 children (1.3%) with ALL than among 507 control children (0.2%).(201) However, the total number of exposed children was small and the difference in relative frequency was not statistically significant.

In a Danish study, among 55,120 newborns, 9% received phototherapy, which consisted of irradiation with light at wavelengths of 420-470 nm.(189) Linkage of the birth cohort with the national cancer registry revealed 34 children with leukemia (28 with ALL), and no excess risk among those receiving neonatal phototherapy (SIR 1.2, 95% CI 0.8-1.7). Subgroup analyses revealed no remarkable patterns for any category of leukemia subtype, gender, or age at diagnosis (follow-up age of up to 14 years). In a British study, leukemic cases appeared to be comparatively robust at birth with respect to the ORs for jaundice, phototherapy, admission to special care nursery and neonatal intensive care all being less than 1.0.(60) Cnattingius et al found that both physiological jaundice (OR 2.5; 95% CI 1.2-5.0) and phototherapy (OR 7.5; CI 1.8-31.9) were associated with myeloid leukemia.(202)

An increased risk of childhood leukemia associated with neonatal jaundice, particularly among infants receiving phototherapy, has been previously reported.(160) (203) (202) Exclusion of infants with DS has previously been shown to alter the association between neonatal jaundice and childhood leukemia indicating that the strong association between DS and childhood leukemia may account for some of the positive associations found in earlier studies.(202) The finding of a study by Podvin et al that infants with jaundice who remained in the hospital > 5 days are at an increased risk of childhood leukemia, even after exclusion

of those with DS, has not been previously reported. These investigators recommend that physiological mechanisms that explain the association between neonatal jaundice and childhood leukemia should continue to be explored.(71)

2.5 Discussion

The evidence on the role of phototherapy in leukemogenesis is more limited than is the case for oxygen, but is nonetheless suggestive. Many studies of childhood cancer retrieve delivery records as part of data collection; this encourages any investigator who has access to such data to examine the history of oxygen supplementation. Spector et al recommend that special consideration be given to the association of oxygen with leukemia in preterm infants.(163) Future large studies should also assess this association with particular attention to strata of the study subjects with high fetal growth (FG).

Chapter 3: NEONATAL OXYGEN SUPPLEMENTATION, PHOTOTHERAPY AND RISK OF ACUTE LYMPHOCYTIC LEUKEMIA

3.1 Introduction

Our study had four aims: the first three were to examine the association of three exposures of interest with ALL – neonatal oxygen supplementation, neonatal phototherapy, and maternal oxygen exposure. The fourth aim was to use multivariate methods to address potential confounding of the above associations by other perinatal circumstances. The significance of this research lies in the possibility of finding alterable risks for ALL. It is well known in obstetric and neonatal circles that the use of oxygen and phototherapy could be restricted to levels below those currently in use without harm to subjects. Thus, if the treatments we examine increase the risk of leukemia, it should be possible to find alternative ways to manage newborn problems that minimize exposure to these treatments.

3.2 Materials and methods

This study is Phase II of a larger study on perinatal factors and ALL in Michigan. We received approval from the Community Research Institutional Review Board (CRIRB) at Michigan State University (MSU) for both phases of the study. This community research board covers MSU, Michigan Department of Community Health (MDCH) and several hospitals with which we worked, thus simplifying the efforts needed to obtain IRB approvals. Since this study involved data collection at both state and hospital levels, we initiated a process of regular communication with the CRIRB, MDCH, and IRBs in 12 hospitals to ensure that we addressed all matters of concern with respect to security and

quality of data collected from throughout the state. We also formed a neonatology advisory group consisted of senior neonatologists from designated hospitals.

In Phase I, all children (n =1,021) with histologically-confirmed ALL diagnosed under 10 years of age in the State of Michigan between 1985 and 2003 were ascertained in the population-based Michigan Cancer Registry. Records of the cases born in Michigan were linked by the MDCH to their birth certificates. From the birth certificate files, the MDCH randomly selected two surviving (to age one year) children as controls for each case, matched on hospital of birth, gestational age (GA +/- two weeks), sex, month and year of birth. The linked (live birth-cancer-inpatient) data were anonymized and sent to us by the MDCH. We examined the matching on GA and sex, and confirmed the accuracy of these matching procedures.

The final step in the first phase of the study was to assess the relationship of birth certificate variables of interest with ALL. Hardly any birth certificate variable could shed light on our hypotheses of interest, which is why we needed to abstract hospital records. The MDCH developed lists of cases and matched controls, and separated them into files so that they could be requested by the hospitals. These files contained the hospital record numbers (recorded in Michigan on birth certificates). Upon the finalization of hospital IRB approval, the MDCH directly sent the files to our on-site research collaborators to locate and obtain medical records for our hospital chart abstractors. Our research team thus remained masked to any identifying information on study subjects.

The second phase of the research involved medical record abstraction on a subset of cases, those born at 12 delivery services in Michigan, along with their matched controls, who, because of our matching algorithm, were born in the same hospital. The designated hospitals were chosen largely for efficiency because they are the largest maternity hospitals in the state. They cover > 30% of live births registered in Michigan during the study period. Our designated hospitals also included some smaller hospitals that were affiliated with the CRIRB enabling us to obtain hospital IRB approval through an expedited process. A list of the hospitals is provided below:

- Beaumont Hospital (Royal Oak, Troy)
- Sparrow Hospital (Lansing)
- Ingham Regional Medical Center (Lansing)
- Bronson Methodist Hospital (Kalamazoo)
- Borgess Medical Center (Kalamazoo)
- Spectrum Health Medical Center, including Butterworth, Blodgett and Helen DeVos Children's hospitals (Grand Rapids)
- Metro Health Hospital (Grand Rapids)
- Covenant Health Care (Saginaw)
- Hurley Medical Center (Flint)
- Hutzel Women's Hospital (Detroit)
- Henry Ford Hospital (Detroit)
- St. John Hospital and Medical Center (Detroit)

This study involved the following data collection and data management steps:

(a) Identifying a collaborating neonatologist at the study hospital;

(b) Obtaining approval from the hospital IRB;

(c) Identifying whether the hospital would require us to use an in-house abstraction service supervised by their research office, or would permit our trained abstractors to abstract records;

(d) Developing medical record abstraction forms to obtain information on the exposures of interest and potentially confounding variables;

(e) Locating medical records of cases, controls and their mothers;

(f) Hiring and training personnel to perform the record abstractions. We hired medical students and nurses because of their familiarity with medical terminology; all were trained by a very skilled nurse-researcher;

(h) Pretesting the abstraction forms with a variety of newborn and maternal record types with varying levels of complexity of oxygen exposure;

(i) Developing, in collaboration with Biomedical Research Informatics Core (BRIC) at MSU, a system for online recording of the abstraction process; and

(j) Developing, also with BRIC, a format for archiving the entire database, with data from both birth certificates and hospital records, for future use.

We produced a working on-line abstraction system with an easy-to-use form which was used successfully by a number of medical students trained in our protocol. In some hospitals, our team performed medical record abstraction; in others, this work was performed by experienced research nurses employed by the hospitals, and working under our supervision. Samples of records were abstracted in duplicate to assess reliability. The process of our communication with study hospitals was very time-intensive and laborious, and involved

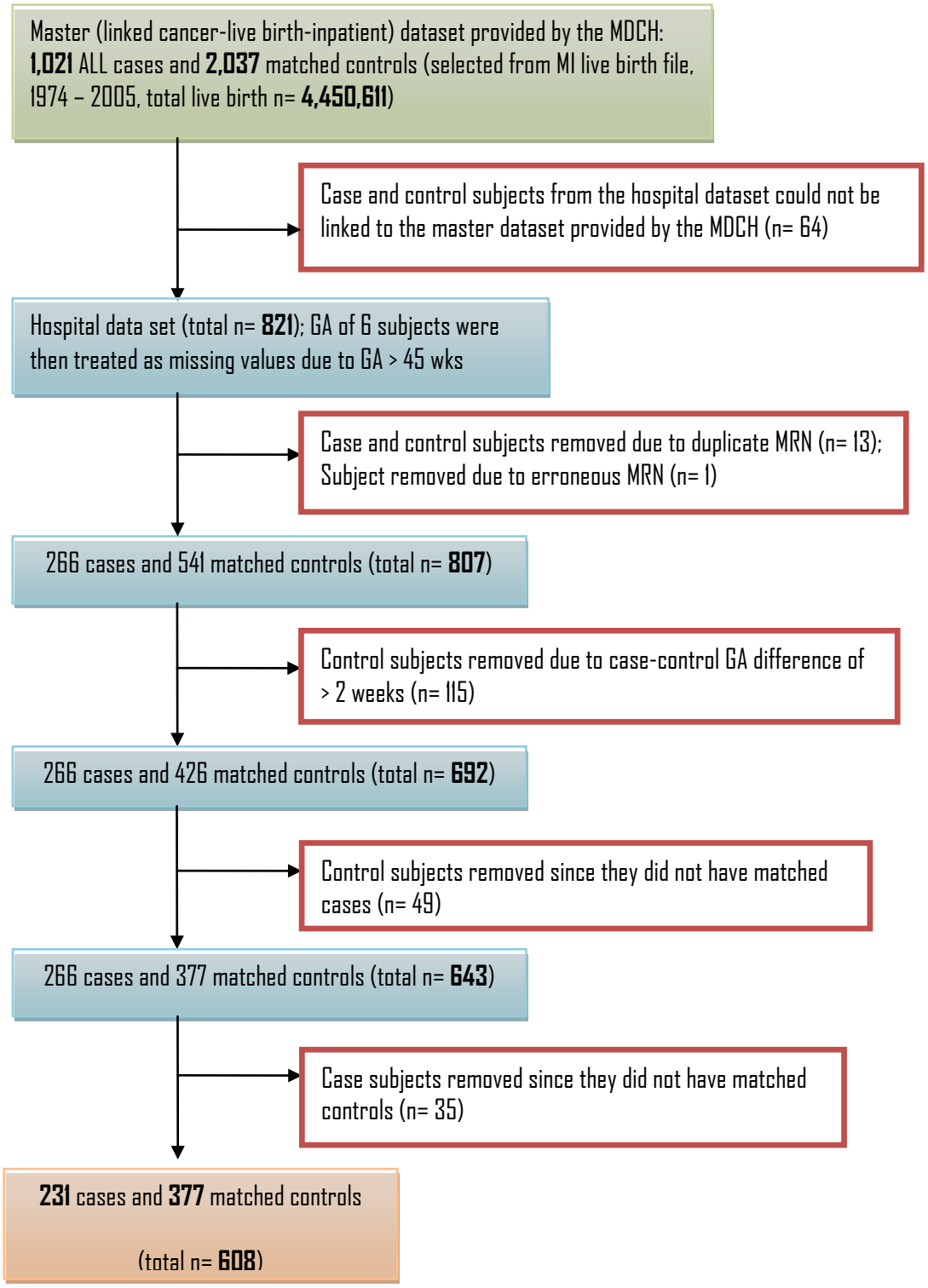
several stakeholders, including clinician collaborators, hospital IRBs and research coordinators.

We arranged to have the MSU BRIC upload (de-identified) birth records, cancer registry data, and patient discharge records onto their data management system RIX, linking subjects via a pre-existing master record number (MRN; provided by the MDCH). As it could not always be possible to find hospital records, especially those of cases and controls from earlier years, the number of cases and matched controls in the hospital record dataset is smaller than the nearly 3,000 used in the birth certificate analysis.

Figure 3-1 includes a diagram showing the data cleaning procedure of the study. In Phase I, the MDCH provided us with a linked dataset including data on 1,021 cases and 2,037 matched controls. The live birth pool used for matched control selection (n= 4,450,611) excluded deaths and non-Michigan births for the period 1974-2005. Our initial hospital record dataset included data for a total of 885 cases and matched controls. Six subjects were removed since they did not meet our inclusion criteria (GA of 20-45 weeks, and BW of 500-6,000 g). We were able to link hospital data to the Michigan linked data for 821 subjects. Thirteen subjects were manually removed since they had the same (duplicate) MRN (linkage variable). One subject was removed due to an erroneous MRN. Out of 807 subjects (266 cases and 541 controls), 115 (control) subjects had GA greater than 2 weeks compared to their matched cases. After excluding these controls, the total sample size dropped to 692 (266 cases and 426 controls). Forty-nine (control) subjects did not have matched cases, therefore were excluded. Thirty-five cases did not have matched controls, therefore were

removed. Our final dataset had a total of 608 subjects (231 cases and 377 controls). Each case had at least one matched control; most cases had two matched controls.

Figure 3-1 Flow chart of Michigan linked (cancer-live birth-inpatient) data cleaning



For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation.

To measure FG, we calculated fetal growth ratio (FGR) by dividing each subject's BW by median BW of the control population for the same gestational week. Univariate and multivariate statistical analyses using conditional logistic regression were performed to study the association between ALL and exposure to supplementary oxygen, phototherapy and other perinatal factors of interest. Maximum likelihood estimates of OR, p-value and 95% CI were obtained, taking into account potential confounding factors. Regression analysis in SAS statistical program (version 9.1; SAS Institute Inc., Cary, NC) was used to fit conditional logistic model in this 1:2 matched case–control study. The p-values reported in tables 3-7 and 3-8 were obtained using unconditional logistic regression. All tests of hypotheses were two-sided at significance level alpha =.05.

3.3 Results

Figures 3-2, 3-3 and 3-4 show BW, GA and FGRs of ALL cases and matched controls. As expected, mean BW was higher among cases (3,461 vs. 3,372 g; mean difference = 89 g). There was only a very slight difference between GA of the cases and controls, because we matched on GA. Figure 3-4 shows that FGR is relatively higher among ALL cases than matched controls.

Figure 3-2 Birth weight distribution of ALL cases and matched controls, hospital data

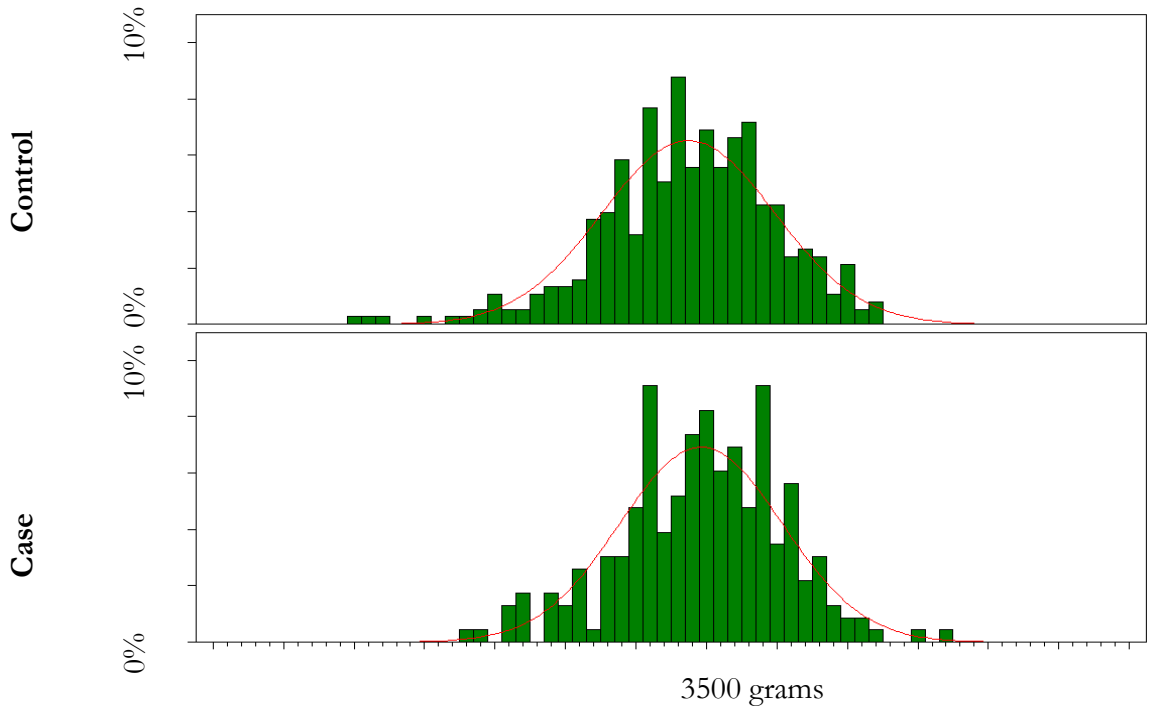


Figure 3-3 Gestational age distribution of ALL cases and matched controls, hospital data

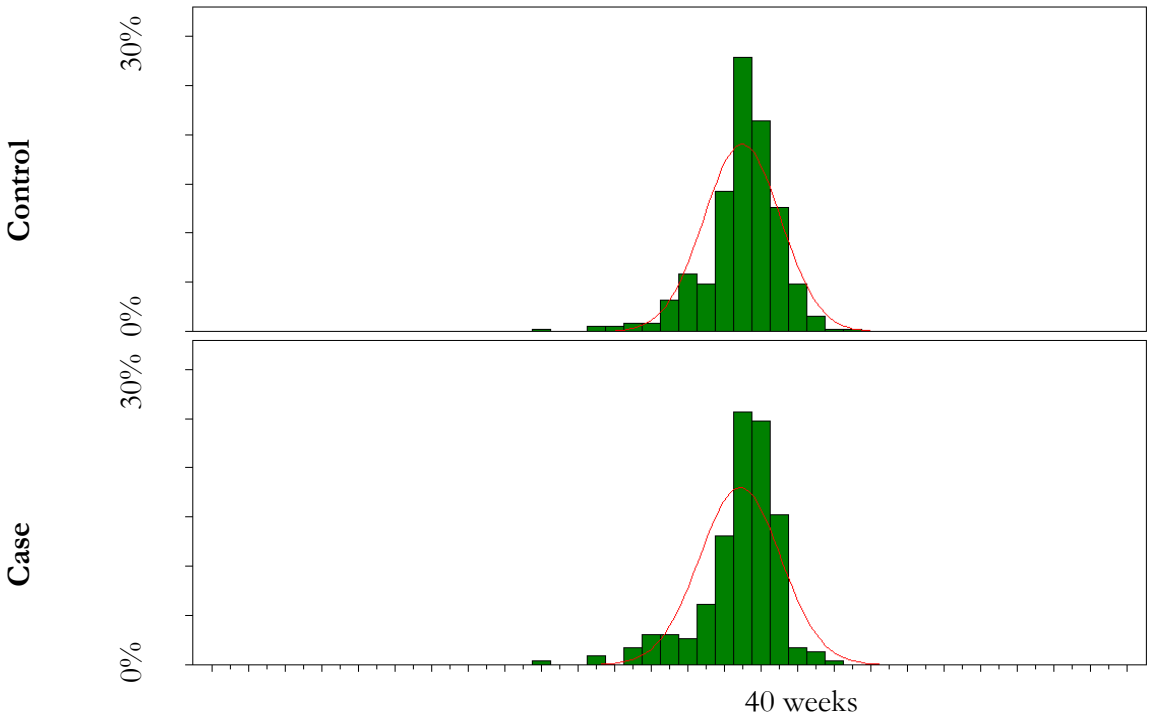
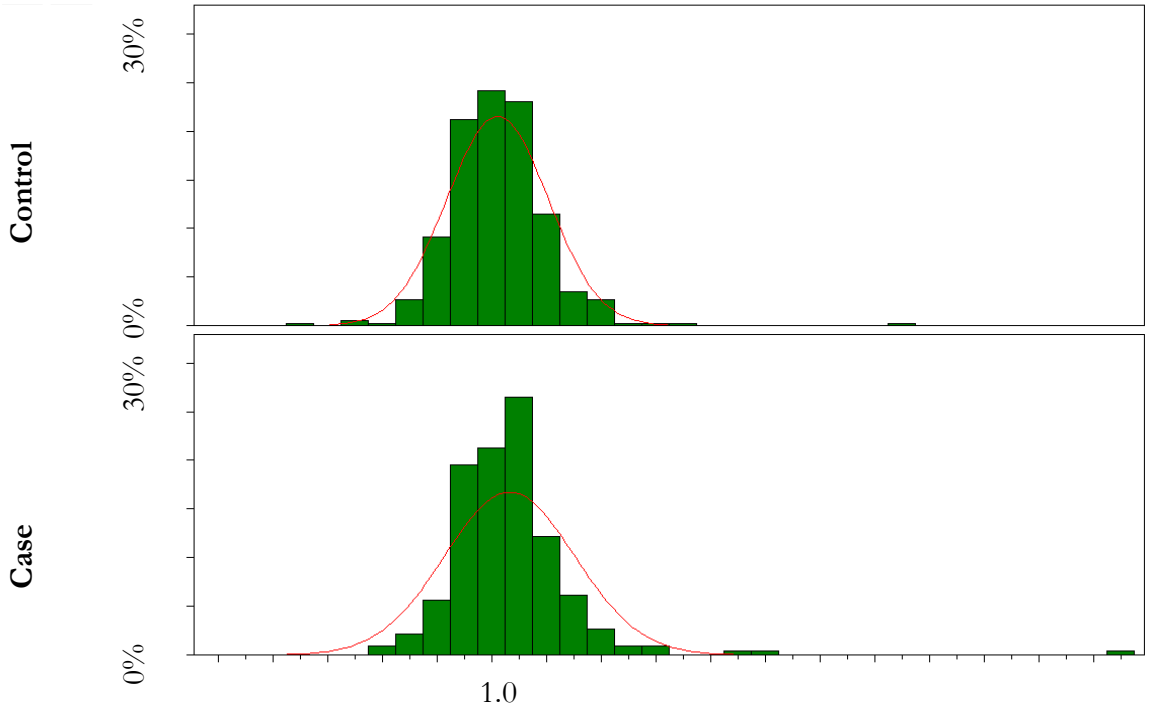


Figure 3-4 Fetal growth ratio (FGR) distribution of ALL cases and matched controls, hospital data



Tables 3-1 and 3-2 show crude ORs for infant exposure to oxygen and risk of ALL. We distinguished oxygen exposure in delivery room and after delivery room, as the two forms of exposure often differ in duration and mode of administration. There was no excess risk of ALL due to oxygen exposure (OR 0.8, CI 0.56-1.15) and no significant OR for any level of oxygen exposure in delivery room. However, the OR for oxygen exposure post delivery room was 1.61 (CI 0.93-2.77). With 3 levels of oxygen exposure post delivery room (0 as reference), the ORs for oxygen exposure > 3 minutes and ≤ 3 minutes were 1.95 (CI 0.92-4.13) and 2.56 (CI 0.57-11.47), respectively.

Table 3-1 Infant exposure to oxygen in delivery room and risk of ALL

		Case	Control	OR, 95%CI
N of infants available for analysis		**222**	**362**	
Oxygen exposure	Yes	78 (35.1%)	147 (40.6%)	0.80 (0.56, 1.15)
	No	144 (64.9%)	215 (59.4%)	
Duration (t) of oxygen exposure (5 levels; in minutes)	> 3	12 (5.4%)	19 (5.3%)	0.96 (0.44, 2.12)
	$2 \leq t \leq 3$	4 (1.8%)	5 (1.4%)	1.56 (0.37, 6.47)
	$1 \leq t < 2$	4 (1.8%)	6 (1.7%)	0.93 (0.22, 4.03)
	$0 < t < 1$	7 (3.1%)	11 (3.0%)	1.20 (0.40, 3.54)
	0 (ref)	195 (87.8%)	321 (88.7%)	1.0
Duration of oxygen exposure (3 levels)	> 3	12 (5.4%)	19 (5.2%)	0.97 (0.44, 2.14)
	$0 < t \leq 3$	15 (6.8%)	22 (6.1%)	1.20 (0.57, 2.56)
	None (ref)	195 (87.8%)	321 (88.7%)	1.0
Duration of oxygen exposure (2 levels)	> 3	12 (5.4%)	19 (5.2%)	0.96 (0.44, 2.11)
	≤ 3 (ref)	210 (94.6%)	343 (94.8%)	1.0

Table 3-2 Infant exposure to oxygen post delivery room and risk of ALL

		Case	Control	OR, 95%CI
N of infants available for analysis		**231**	**377**	
Oxygen exposure	Yes (a)	39 (16.9%)	46 (12.2%)	1.61 (0.93, 2.77)
	No	192 (83.1%)	331 (87.8%)	
Duration (t) of oxygen exposure (5 levels; in minutes) (b)	> 3	19 (8.8%)	22 (6.1%)	1.76 (0.83, 3.74)
	$2 \leq t \leq 3$	3 (1.4%)	0	-
	$1 \leq t < 2$	2 (0.9%)	2 (0.6%)	1.55 (0.17, 13.92)
	$0 < t < 1$	1 (0.5%)	3 (0.8%)	0.62 (0.05, 7.40)
	0 (ref)	192 (88.5%)	331 (92.5%)	1.0
Duration of oxygen exposure (3 levels)	> 3	19 (8.8%)	22 (6.1%)	1.95 (0.92, 4.13)
	$0 < t \leq 3$	6 (2.8%)	5 (1.4%)	2.56 (0.57, 11.47)
	None (ref)	192 (88.5%)	331 (92.5%)	1.0
Duration of oxygen exposure (2 levels)	> 3	19 (8.8%)	22 (6.1%)	1.79 (0.86, 3.74)
	≤ 3 (ref)	198 (91.2%)	336 (93.9%)	1.0

(a) For 7 (of 39) cases and 6 (of 46) controls, there were records of chart abstraction related to duration of oxygen therapy only (with no record of oxygen exposure as yes/no) post delivery room. These observations were treated as exposed to oxygen.

(b) Data related to the duration of oxygen exposure post delivery room for the first 3 days after birth were abstracted from hospital charts; we grouped the observations based on maximum duration of oxygen exposure on any day of the 3 days after birth.

Most, but not all, post-delivery room exposure to oxygen occurred because of admission to a newborn intensive care unit (NICU). Although babies who subsequently developed ALL were of the same GA and even better grown than controls, they were 50% more likely to be admitted to NICU, a finding which was at the edge of statistical significance (Table 3-3).

Table 3-3 NICU admission and risk of ALL

		Case	Control	OR, 95%CI
Admission to NICU				
N of infants available for analysis		**231**	**377**	
Newborn intensive care	Yes	33 (14.3%)	37 (9.8%)	1.55
	No (ref)	198 (85.7%)	340 (90.2%)	(0.88, 2.73)

Table 3-4 shows that a non-significant OR of 0.73 (CI 0.47-1.15) for maternal oxygen exposure and risk of ALL. There was only a hint of a gradient with an OR of 0.66 (CI 0.36-1.23) for maternal oxygen exposure ≥ 30 minutes.

Table 3-4 Maternal exposure to oxygen and risk of ALL

		Case	Control	OR, 95% CI
N of mothers available for analysis		**182**	**295**	
Maternal oxygen exposure	Yes	63 (34.6%)	117 (39.7%)	0.73 (0.47, 1.15)
	No (ref)	119 (65.4%)	178 (60.3%)	
N of mothers available for analysis		**159**	**255**	
Duration of oxygen exposure (4 levels; in minutes)	30+	23 (14.5%)	47 (18.4%)	0.66 (0.36, 1.23)
	15-29	9 (5.7%)	18 (7.1%)	0.70 (0.28, 1.75)
	1-14	8 (5.0%)	12 (4.7%)	0.96 (0.35, 2.67)
	None (ref)	119 (74.8%)	178 (69.8%)	1.0
Duration of oxygen exposure (3 levels)	30+	23 (14.5%)	47 (18.4%)	0.66 (0.35, 1.22)
	1-29	17 (10.7%)	30 (11.8%)	0.80 (0.39, 1.63)
	None (ref)	119 (74.8%)	178 (69.8%)	1.0

Table 3-5 shows a non-significant OR of 0.88 (CI 0.44-1.74) for infant phototherapy and risk of ALL. Outpatient phototherapy and jaundice after discharge from hospital were unknown to us.

Table 3-5 Infant phototherapy and risk of ALL

		Case	Control	OR, 95% CI
N of infants available for analysis		**231**	**377**	
Infant photo therapy	Yes	15 (6.5%)	27 (7.2%)	0.88 (0.44,1.74)
	No (ref)	216 (93.5%)	350 (92.8%)	1.0
Duration of photo therapy (in hours)	24+	9 (3.9%)	19 (5.0%)	0.67 (0.27,1.66)
	< 24 (ref)	222 (96.1%)	358 (95.0%)	1.0

As Table 3-6 shows, BW was significantly higher (p=0.0371) among ALL cases (3,461 g).than matched controls (3,372 g). There was 41% excess risk of ALL (CI 1.02-1.94) for each 1,000 g increase in BW. The excess risk was 26% (CI 1.08, 1.47) for a 5-year increase in maternal age, and 27% (CI 1.00, 1.60) for each additional X-ray exposure. There was only a slight (< 1 cm) difference between birth length of the cases and controls.

This table also shows unadjusted ORs for select neonatal and maternal factors and risk of ALL. The following categorical variables had significant ORs for risk of ALL: BW ≥ 4,000 g (1.34, CI 0.83-2.18; NBW as reference), and maternal black race (0.30, CI 0.14-0.66). Neonatal exposure to X-ray had an OR of 1.73 (CI 0.99-3.04) with borderline statistical significance (p=.0547). Neonatal jaundice observed in the first 24 hours after birth had an OR of 1.92 (CI 0.97-3.79) with borderline significance (p=0.0601). Odds ratio for Apgar score at one minute (0-6 vs 7-10) and risk of ALL was 1.03 (CI 0.56-1.92); OR for Apgar score at 5 minutes (0-6 vs 7-10) was 0.50 (CI 0.10-2.52).

Table 3-6 Frequencies and crude odds ratios for birth characteristics, maternal factors, and risk of ALL

Variable		Case N=231	Control N=377	Odds ratio (95% CI) (a)	P-value
		Mean (SD)	Mean (SD)		
Maternal Age (y)		28.0 (5.7)	26.7 (5.8)		.0032
	1 year increase			**1.05 (1.02, 1.08)**	
	5 year increase			**1.26 (1.08, 1.47)**	
Average number of cigarettes per day smoked during pregnancy		3.3 (7.2)	2.7 (6.1)		.7056
	1 cigarette increase			1.01 (0.98, 1.05)	
	10 cigarette increase			1.15 (0.80, 1.64)	
Birth weight (g)		3461 (577)	3372 (613)		.0371
	1,000 g increase			**1.41 (1.02, 1.94)**	
Birth length (cm)		50.2 (4.4)	49.4 (6.0)		.9311
	10 cm increase			0.96 (0.43, 2.18)	
Head circumference (cm)		34.1 (2.5)	34.1 (2.2)		.4543
	1 cm increase			1.04 (0.94, 1.16)	
Number of X-ray		0.3 (1.2)	0.1 (0.6)		.0459
	1 X-ray count increase			**1.27 (1.00, 1.60)**	
		N (%)	**N(%)**		
Birth weight (g)	500–2,499	16 (6.9%)	28 (7.4%)	0.86 (0.39, 1.86)	.4401
	2,500–3,999	177 (76.6%)	300 (79.6%)	1.0	
	4000 +	38 (16.5%)	49 (13.0%)	1.34 (0.83, 2.18)	
Maternal asthma	Yes	7 (3.0%)	16 (4.2%)	0.67 (0.27, 1.66)	.3875
	No (ref)	224 (97.0%)	361 (95.7%)	1.0	
Tobacco use (during pregnancy)	Yes	38 (25.2%)	59 (25.5%)	1.01 (0.58, 1.73)	.9816
	No (ref)	113 (74.8%)	172 (74.5%)	1.0	
Average number of cigarettes smoked per day (all trimesters)	None (ref)	113 (77.4%)	172 (80.7%)	1.0	.9241
	1-9	7 (4.8%)	6 (2.8%)	1.14 (0.36, 3.57)	
	10+	26 (17.8%)	35 (16.4%)	1.12 (0.58, 2.15)	
Maternal race	White (ref)	209 (90.5)	313 (83.0)	1.0	.0083
	Black	15 (6.5)	50 (13.3)	**0.30 (0.14,0.66)**	
	Others	7 (3.0)	14 (3.7)	0.68 (0.26, 1.77)	

Table 3-6 (cont'd)

Apgar score at 1 min	0-6	20 (8.7)	30 (8.0)	1.03 (0.56, 1.92)	.9156
	7-10 (ref)	210 (91.3)	343 (92.0)	1.0	
Apgar score at 5 min	0-6	2 (0.9)	6 (1.6)	0.50 (0.10, 2.52)	.4012
	7-10 (ref)	228 (99.1)	365 (98.4)	1.0	
Meconium stained fluid	Yes	39 (19.2%)	66 (20.2%)	0.87 (0.54 1.39)	.5664
	No (ref)	164 (80.8%)	261 (79.8%)	1.0	
Vaginal delivery	Yes	177 (76.6%)	283 (76.3%)	1.04 (0.69, 1.56)	.8494
	No (ref)	54 (23.4%)	88 (23.7%)	1.0	
Method of delivery	Vaginal without assistance (ref)	150 (72.5%)	250 (73.5%)	1.0	.2492
	Vaginal with assistance	27 (13.0%)	33 (9.7%)	1.58 (0.89, 2.82)	
	C-section	30 (14.5%)	57 (16.8%)	0.93 (0.54, 1.60)	
Exposed to X-ray	Yes	31 (13.4%)	32 (8.5%)	1.73 (0.99, 3.04)	.0547
	No (ref)	200 (86.6%)	345 (91.5%)	1.0	
Number of X-rays	0 (ref)	200 (86.6)	345 (91.5)	1.0	.1578
	1	18 (7.8)	19 (5.0)	1.74 (0.86, 3.51)	
	2+	13 (5.6)	13 (3.4)	1.73 (0.75, 3.96)	
Jaundice observed after birth	Yes	75 (32.5%)	118 (31.3%)	1.16 (0.79, 1.70)	.4577
	No (ref)	156 (67.5%)	259 (68.7%)	1.0	
Jaundice observed in the first 24 hours after birth	Yes	22 (9.5%)	21 (5.6%)	1.92 (0.97, 3.79)	.0601
	No (ref)	209 (90.5%)	356 (94.4%)	1.0	

(a) ORs obtained from conditional logistic regression; significant ORs bolded

Tables 3-7 and 3-8 show p-values and crude ORs for the association of neonatal/ maternal factors and exposure to oxygen (for all cases and controls combined). The following

continuous variables were significantly different between the cases and controls who were exposed to neonatal oxygen supplementation and those who were not: GA ($p < .0001$), BW ($p < .0001$), Apgar score at one minute ($p < .0001$), Apgar score at 5 minutes ($p < .0001$), number of X-rays ($p < .0001$), and maternal age ($p = .0297$).

There were significant ORs for the following categorical variables: multiple births (5.74, CI 2.11-15.61), abnormal birth presentation (3.86, CI 1.96-7.61), Apgar score at one minute of 0-6 (3.80, CI 2.01-7.20), Apgar score at 5 minutes of 0-6 (19.81, CI 3.93-99.88), Cesarean delivery (3.53, CI 2.01-6.22), neonatal exposure to X-ray (13.5, CI 7.6-24.1), single exposure to X-ray (6.90, CI 3.36-14.16), multiple (≥ 2 times) exposure to X-ray (42.5, CI 15.3-117.7), neonatal jaundice (4.70, CI 1.69-13.04), jaundice in the first 24 hours after birth (2.28, CI 1.10-4.72), and premature labor (7.36, CI 4.07-13.31).

These ORs show that there are significantly strong associations between neonatal oxygen exposure, and several conditions of delivery (multiple births, abnormal birth presentation, C-section, premature labor), the newborn (low Apgar score, jaundice) and management (X-rays).

Table 3-7 Frequencies and crude odds ratios for the association of neonatal oxygen exposure post delivery room and neonatal factors

Variable	Neonatal oxygen exposure N=85		No neonatal oxygen exposure N=523		Odds ratio (95%CI) (a)	P-value
	N	**Mean (SD)**	**N**	**Mean (SD)**		
Gestational age (week)	84	38.00 (2.97)	519	39.07 (1.94)		<.0001
1 week increase					**0.82 (0.74, 0.90)**	
Birth weight (g)	85	3159 (830)	523	3446 (545)		<.0001
100 g increase					**0.93 (0.89, 0.96)**	
1,000 g increase					**0.47 (0.32, 0.68)**	
Head circumference (cm)	62	33.63 (2.76)	389	34.15 (2.26)		.1161
cm increase					0.92 (0.84, 1.02)	
Length (cm)	54	48.58 (4.72)	239	49.96		.1046
10 cm increase				(5.65)	0.68 (0.43, 1.08)	
Apgar score at 1 min	83	7.28 (1.87)	520	8.08 (1.13)		<.0001
1 unit increase					**0.70 (0.61, 0.81)**	
Apgar score at 5 min	84	8.50 (1.23)	517	9.00 (0.52)		<.0001
1 unit increase					**0.45 (0.32, 0.62)**	
Number of X-rays	85	1.02 (1.98)	523	0.06 (0.29)		<.0001
1 X-ray count increase					**5.45 (3.48, 8.53)**	

Table 3-7 (cont'd)

		N (%)	N (%)		
Infant race:	White (ref)	76 (89.4)	446 (85.3)	1.0	.5596
	Black	6 (7.1)	59 (11.3)	0.69 (0.28, 1.65)	
	Other	3 (3.5)	18 (3.4)	0.64 (0.19, 2.13)	
Birth:	Singleton (ref)	75 (89.3)	514 (98.5)	1.0	.0006
	Multiple births	9 (10.7)	8 (1.5)	**5.74 (2.11, 15.61)**	
Birth presentation:					<.0001
	Abnormal presentation	15 (17.6)	27 (5.3)	**3.86 (1.96, 7.61)**	
	Vertex and not recorded (NR) combined (ref)	70 (82.3)	486 (94.7)	1.0	
Meconium stained fluid: Yes		16 (23.2)	89 (19.3)	1.26 (0.69, 2.31)	.4511
	No (ref)	53 (76.8)	372 (80.7)	1.0	
Apgar score at 1 min: 0-6		17 (20.5)	33 (6.3)	**3.80 (2.01, 7.20)**	<.0001
	7-10 (ref)	66 (79.5)	487 (93.6)	1.0	
Apgar score at 5 min: 0-6		6 (8.4)	2 (0.4)	**19.81 (3.93, 99.88)**	<.0001

Table 3-7 (cont'd)

	7-10 (ref)	65 (91.6)	528 (99.6)	1.0	
Delivery type:					<.0001
	Vaginal delivery without assistance (ref)	32 (52.5%)	368 (75.7%)	1.0	
	Vaginal delivery with assistance	5 (8.2%)	55 (11.3%)	0.97 (0.39, 2.40)	
	C-section	24 (33.3%)	63 (13.0%)	**3.53 (2.01, 6.22)**	
Exposure to X-ray:	Yes	36 (50.0)	27 (5.0)	**13.5 (7.6, 24.1)**	<.0001
	No (ref)	36 (50.0)	509 (95.0)	1.0	
Number of X-rays:	0 (ref)	36 (50.0)	509 (95.0)	1.0	<.0001
	1	15 (20.8)	22 (4.1)	**6.90 (3.36, 14.16)**	
	2+	21 (29.2)	5 (0.9)	**42.5 (15.3, 117.7)**	
Neonatal jaundice:	Yes	38 (52.8)	155 (28.9)	**4.70 (1.69, 13.04)**	.0030
	No (ref)	34 (47.2)	381 (71.1)	1.0	
Jaundice in the first 24 h:	Yes	11 (15.3)	32 (6.0)	**2.28 (1.10, 4.72)**	.0263
	No (ref)	61 (84.7)	504 (94.0)	1.0	

(a) ORs obtained from unconditional logistic regression; significant ORs bolded

Table 3-8 Frequencies and crude odds ratios for the association of maternal factors and neonatal oxygen exposure post delivery room

Variable		Neonatal oxygen exposure N=85		No neonatal oxygen exposure N=523		Odds ratio (95%CI) (a)	p-value
		N	**Mean (SD)**	**N**	**Mean (SD)**		
Maternal age (y)		83	28.47 (5.35)	512	26.97 (5.86)		.0297
1 y increase						**1.05 (1.00, 1.09)**	
Number of prior live births		83	0.99 (0.82)	516	0.98 (1.05)		.4083
1 live birth increase						1.01 (0.80, 1.26)	
			N (%)		**N (%)**		
Maternal race:	White (ref)		76 (89.4)		446 (85.3)	1.0	.5118
	Black		6 (7.1)		59 (11.3)	0.60 (0.25, 1.43)	
	Other		3 (3.5)		18 (3.4)	0.98 (0.28, 3.40)	
Prior live births:	0 (ref)		26 (31.3)		199 (38.6)	1.0	.4520
	1		34 (41.0)		189 (36.6)	1.38 (0.80, 2.38)	
	2+		23 (27.7)		128 (24.8)	1.37 (0.75, 2.51)	

Table 3-8 (cont'd)

Tobacco use during pregnancy:	Yes	19 (32.8)	78 (24.1)	1.54 (0.84, 2.81)	.1638
	No (ref)	39 (67.2)	246 (75.9)	1.0	
Premature labor (<37 w):	Yes	26 (31.3)	30 (5.8)	**7.36 (4.07, 13.31)**	<.0001
	No (Ref)	57 (68.7)	484 (94.2)	1.0	

(a) ORs obtained from unconditional logistic regression; significant ORs bolded

Tables 3-9 and 3-10 show adjusted ORs for duration of oxygen supplementation (3+ vs. <3 min) and risk of ALL. We included the following variables in multivariate models: maternal age and race because of their known (and here replicated) associations with ALL, and any variable that we considered a potential confounder because of its association with both oxygen exposure and ALL (X-ray exposure, early neonatal jaundice, and Apgar score at 5 minutes) as demonstrated by having an OR $\geq$ 1.5 (or OR $\leq$ 0.6) with both ALL (Table 3-6) and oxygen (tables 3-7 and 3-8).

After adjustment for potential confounders, ORs for duration of oxygen supplementation (3+ vs < 3 min) in delivery room and post delivery room were 1.03 (CI 0.42-2.56) and 1.16 (CI 0.46-2.91), respectively. The p-value for interaction between oxygen exposure and maternal race was not significant (p=0.999). This could be due to the fact that none of the ALL cases whose maternal race was recorded as black or other (non-white) had been exposed to oxygen in post-delivery room.

Table 3-9 Adjusted odds ratios for duration of oxygen therapy in delivery room, confounding factors, and risk of ALL

Variable	Level	OR (a), 95% CI	p-value
Duration of oxygen (min)	3+ vs. < 3	1.03 (0.42, 2.56)	.9438
Neonatal X-ray exposure (b)	Yes vs. No (ref)	1.82 (0.97, 3.39)	.0601
Jaundice in the first 24 hours	Yes vs. No (ref)	1.55 (0.72, 3.33)	.2630
Maternal age	Continuous	1.04 (1.00, 1.07)	.0413
Apgar score at 5 min	0-6 vs. 7-10 (ref)	0.25 (0.03, 2.47)	.2373
Maternal race	Black vs. White (ref)	0.29 (0.12, 0.73)	.0238
	Other vs. White	0.68 (0.24, 1.91)	

(a) Adjusted for all variables listed in the table

(b) After removing the variable, jaundice in the first 24 hours after birth, OR for X-ray exposure became significant (OR 1.88, CI 1.01-3.48).

Table 3-10 Adjusted odds ratios for duration of oxygen therapy post delivery room, confounding factors, and risk of ALL

Variable	Level	OR (a), 95% CI	p-value
Duration of oxygen post delivery room (min)	3+ vs. < 3	1.16 (0.46, 2.91)	.7494
Neonatal X-ray exposure (b)	Yes vs. No (ref)	1.81 (0.85, 3.86)	.1230
Jaundice in the first 24 hours	Yes vs. No (ref)	1.47 (0.66, 3.27)	.3425
Maternal age	Continuous	1.03 (1.00, 1.07)	.0631
Apgar score at 5 min	0-6 vs. 7-10 (ref)	0.27 (0.03, 2.68)	.2627
Maternal race	Black vs. White (ref)	0.29 (0.11, 0.73)	.0180
	Other vs. White	0.56 (0.18, 1.70)	

(a) Adjusted for all variables listed in the table

(b) After removing the variable, jaundice in the first 24 hours after birth, OR for X-ray exposure remained insignificant (OR 1.81, CI 0.85-3.85).

3.4 Discussion

3.4.1 Oxygen therapy

We did not confirm any of the study hypotheses related to neonatal/ maternal oxygen exposure and risk of ALL. However, we were able to show significant associations between a number of factors related to conditions of delivery and newborn and exposure to oxygen post delivery room. We therefore controlled for these factors in our multivariate analyses.

Spector et al considered family SES, maternal education, maternal age (> 35 years), sex of child, race of child (black, white, other), BW, and GA to be potential confounders, because of their known associations with some childhood cancers. They also adjusted for Apgar score at 1 minute, Apgar score at 5 minutes (0 to 6), and the presence of meconium at birth as markers of neonatal distress. Adjustment for each was made in turn, rather than simultaneously, because cases were few.(163) Naumburg et al adjusted for 1-minute Apgar score of 3 or less. Adjustment for other potential confounders (maternal age, smoking and parity) affected their results only marginally.(162)

Newborns, especially if preterm, are particularly susceptible to oxidative stress and damage due to increased generation of ROS, the lack of adequate antioxidant protection, and the inability to induce antioxidant defenses during the hyperoxic challenge at birth.(204) Mongelli et al found that the duration of the second stage of labor was correlated with raised ROS-derived lipid peroxidation products.(205)

A Minnesota study found that one minute Apgar scores ≤ 7 increased risk for both ALL and AML (HR for ALL 1.30, 95% CI 1.05-1.61).(68) The study did not find any association between assisted ventilation and ALL. Our analysis of data available on birth certificates showed no excess risk for infants with low Apgar scores or assisted ventilation, both possible markers of oxygen exposure. Phase I of our study showed that requirement for assisted ventilation, the only birth certificate variable that is directly related to oxygen supplementation was recorded in only 2% of live births (underlining the need to assess hospital records).

The results of Spector's study are consistent with those reported by Naumburg et al.(162) The results of the latter study were based on small numbers (oxygen by mask 3-10 min, 14 cases, 4 controls; OR 3.54, 95% CI 1.16-10.80), therefore chance could not be ruled out. Spector's study was the first in the US assessing association of oxygen supplementation and childhood cancer. However, the data used for this study were not population-based. The CPP enrolled approximately 48,000 women, who had about 60,000 pregnancies, at 12 university-affiliated medical centers between 1959 and 1966.(206) Since phototherapy began to become a standard intervention for the treatment of neonatal jaundice in 1970s it was not included in this study.

3.4.2 Phototherapy

Our study did not find any significant association between neonatal phototherapy and risk of ALL. In a study conducted by van Steensel-Moll et al in the Netherlands,(201) based on stratified analysis of the ALL cases born in hospital, an OR of 3.6 (95% CI 0.9-57.4) was

reported for hospitalization due to neonatal hyperbilirubinemia. As this investigation was not designed to study the association between fluorescent light and childhood leukemia, no detailed information concerning intensity and duration of potential exposures was available. The investigators, therefore, underline, "..to confirm the hypothesis of Ben-Sasson and Davis,(185) epidemiologic studies with specific questions concerning fluorescent light exposure in the neonatal period will be necessary..." To test the hypothesis that exposure to high intensity lightning (around 400 nanometers) in neonatal nurseries increases the incidence of childhood leukemia, over 55,120 newborn children treated with phototherapy for hyperbilirubinemia were identified from the Danish Hospital Discharge Register for 1977-89.(189) The large series of newborns of whom 85 to 90 percent were exposed to intense light during treatment for hyperbilirubinemia revealed no increase in childhood leukemia or other childhood cancers.

One theory proposes that phototherapy treatment of neonatal jaundice causes free radicals to circulate in the newborn, resulting in transformation of lymphoblasts by altering DNA.(185) Although results of the study by Podvin et al supports this hypothesis, it has been challenged by studies that have found no evidence of increased risk of leukemia associated with phototherapy use.(188) (161) (189) (60) (190)

3.4.3 Jaundice

Our study found an association, with borderline significance, between neonatal jaundice in the first 24 hours after birth and risk of ALL. We also found a significant association between jaundice in the first 24 hours after birth and oxygen exposure post delivery room.

This finding could be a possible indication of the confounding role bilirubin plays on the pathway between oxygen and ALL. In fact, as early as 1937, Najib-Farah demonstrated a protective effect of bilirubin in bacterial infections.(179) An increased risk of childhood leukemia associated with neonatal jaundice, particularly among infants receiving phototherapy, has been previously reported. (160) (203) (202) Epidemiological studies and animal experiments have identified bilirubin as a molecule at the crossroads of the protection of the body against ROS.(207) Low, physiological bilirubin concentrations confer potent antioxidant protection via recycling of biliverdin from oxidized bilirubin by biliverdin reductase, linking this sink for oxidants to the NADPH pool.(208)

Roman et al carried out a medical record-based study of ALL diagnosed before the age of 30 years (at three hospitals) in the south of England (113 cases and 226 age- and sex-matched controls). Overall, ALL cases appeared to be comparatively robust at birth with respect to the ORs for jaundice (OR 0.9, CI 0.5-1.7), phototherapy (OR 0.6, CI 0.1-3.4), and admission to neonatal intensive care (OR 0.7, CI 0.2-2.9).(60) Podvin et al, in a study conducted in the State of Washington, reported that the OR for leukemia was greatest among infants with jaundice who received phototherapy during the birth hospitalization (OR 2.2, 95% CI 1.0-4.9), or were hospitalized for > 5 days (OR 2.8, CI 1.4-5.7). As reported by the birth certificate, jaundice was associated with ALL (OR 2.1, CI 1.1-4.0). As reported by hospital discharge codes, the OR for the association of jaundice with ALL was 1.4 (CI 0.8-2.0).(71)

3.4.4 Diagnostic radiation

Our study found an association, with borderline significance, between neonatal exposure to X-ray and risk of ALL. We also found a highly significant association between neonatal X-ray exposure and oxygen exposure post delivery room. This finding could be a possible indication of the confounding role X-ray plays on the pathway between oxygen and ALL.

Compared to the effects of in-utero radiation exposure on childhood cancer, the effects of postnatal diagnostic exposure have been much less studied.(96) (97) A recent German cohort study reported no increase in cancer risk among children and youths with very low radiation doses from diagnostic radiation.(209) (210) A recent British study showed that exposure to diagnostic X-rays in early infancy was associated with small, non-significant excess risks for all cancers and leukemia (OR for ALL 1.41, CI 0.85-2.35).(211) A recent case-control study (711 children aged 0-14 years diagnosed with ALL) in California showed that after excluding X-rays in the year prior to diagnosis (reference date for matched controls), risk of ALL was elevated in children exposed to three or more post-natal X-rays (OR 1.85, 95% CI 1.12-2.79).(212)

In fact, ionizing radiation from X-rays as well as polymorphisms in DNA repair genes are plausible risk factors for childhood leukemia. Infante-Rivard et al conducted a case-control study of childhood ALL measuring reported postnatal X-rays in 701 cases aged 0-14 years and in as many population-based controls matched on age and sex. There was an increase in risk of leukemia with number of X-rays: the adjusted OR for two or more X-rays (vs. none) was 1.48 (95% CI 1.11-1.97). That risk was slightly higher among girls (OR 1.67).(104)

3.4.5 Maternal age

Our study shows that there is a significant association between high maternal age and ALL, a finding consistent with the findings of several other studies.(67) (68) (69) (70) (71) A Swedish study showed that childhood leukemia risk increased with maternal age for mothers born in the past, whereas maternal age had no effect on this risk for mothers born more recently. This finding suggests that leukemia risk may be related to an environmental factor to which women's exposure has changed over time.(213)

3.4.6 Strengths

Despite the rarity of childhood cancers, we could obtain a relatively large sample of cases in the State of Michigan. However, general limitations of case-control studies apply to our study, but the most important limitation, recall bias, did not operate, as our exposure information was collected years prior to the diagnosis. In addition, we believe our relatively diverse and representative study population has several merits. The study population came from all over the state (minimal selection bias), and we conducted hospital record review in identical fashion for cases and controls (minimal information bias).

Although our data were collected in several hospitals with various admission forms, a number of factors contributed to the minimization of information bias at the hospital level. Our medical record abstraction forms were carefully designed and pre-tested. Since in some designated hospitals we had more than one medical student or research nurse involved in record abstraction, we were able to perform double data entry for the purpose of data quality control. At the server level (BRIC), we checked the collected data on a regular basis, and

compared values for select variables from the hospital data with those from the Michigan linked dataset (provided by the MDCH) to detect any possible discrepancies.

The major strength of our study is its design which includes a two-phase approach that allowed us to obtain a matched control sample in the first phase, and to collect detailed information on neonatal and maternal exposures (from medical records) in the second phase, providing high internal validity to our study (minimal measurement bias). Since additional resources (multiple funding) became available, we were fortunate, in the first phase, to obtain data on all ALL cases under 10 years of age in Michigan (to reach an optimal sample size).

We had two strategies for addressing confounding should it occur. First, we matched our controls to cases. The main matching criterion is GA, which is a prime determinant of oxygen use in newborns. Although there is some argument against the idea of adjustment for GA,(214) there are studies which propose that BW corrected for GA is a better predictor than BW alone of risk for ALL.(70) (215) Based on our study design, we were well able to match study controls on GA rather than control for it through multivariate analyses.

Likewise, all controls were born in the same hospitals as cases at about the same time, so that differences in practice patterns across hospitals and over time are not confounding. But we could also adjust in the analysis of our data for any potential confounder, all of which we were able to record. Our abstraction instruments were very careful to obtain information on all conditions we thought could lead to oxygen use in mothers or babies, so that we could take account of those conditions in any analyses we performed.

3.4.7 Limitations

The population-based, state-wide selection of cases and comparable controls suggests that selection bias is unlikely to account for the exposure-outcome associations of interest. Furthermore, exposure data were obtained retrospectively in a standardized fashion for virtually all births. Although some exposures might have been underreported, this underreporting should not differ between cases and controls but would reduce statistical power to detect any effects. As far as infant supplemental oxygen use is concerned, Jurek et al recommend use of multiple measurement sources to allow both cross-checking and synthesis of results into more accurate measures.(216)

In the beginning of our study, it was very difficult to know exactly what would be found in older charts. We designed a form to obtain maximum information on oxygen exposure, but we fully realized that we might have only partial information in many charts. Our collection of oxygen information is more exact and detailed than has been obtained in previous studies, and thus, where information was well recorded, we could know about it. As with any clinical research project, the data could often be insufficient. This is one reason to have a large sample size, and also to abstract data blindly for both cases and controls. Any limitation of data should hold for both groups and therefore not bias the results. Problems with medical records may include incomplete data, and lack of reliability and validity (due to evolving procedures and multiple persons involved in the measurements). Data on various exposures such as smoking are usually recorded poorly unless they are collected in an obligatory manner as part of the routine admissions data collection process.(217)

3.5 Implications

Multi-state studies with very large sample size can provide more details on the important topic covered through our study in Michigan. The results of such studies may influence guidelines for administering oxygen to newborns particularly for long durations of time. As Saugstad mentioned, "…it took more than 30 years from the first observations that oxygen may be toxic during resuscitation till international guidelines changed to recommend that term and near term newborn infants should be resuscitated with air instead of 100% oxygen..." (218)

Chapter 4: FETAL GROWTH, OTHER PERINATAL FACTORS AND RISK OF ACUTE LYMPHOYTIC LEUKEMIA

4.1 Introduction

The literature is consistent in finding that HBW and high rate of FG are linked to ALL.(59, 61, 219-221) In most recent years, few studies have reported a significant association between high FG and ALL.(222-224) This chapter includes the findings of our study with respect to certain perinatal factors, specifically FG and smoking.

4.2 Materials and methods

This study is Phase I of a larger study on perinatal factors and ALL in Michigan. We received approval from the CRIRB at MSU for both phases of the study. This community research board covers MSU, MDCH and several of the hospitals with which we worked, thus simplifying the efforts needed to obtain IRB approvals.

All children (n =1,021) with histologically-confirmed ALL diagnosed under 10 years of age in the State of Michigan between 1985 and 2003 were ascertained in the population-based Michigan Cancer Registry. Records of the cases born in Michigan were linked by the MDCH to their birth certificates. From the birth certificate files, the MDCH randomly selected two surviving (to age one year) children as controls for each case, matched on hospital of birth, gestational age (GA +/- two weeks), sex, month and year of birth.

In the first phase of the study, the MDCH provided us with a linked dataset including data on 1,021 cases and 2,037 matched controls. The live birth pool used for matched control selection (n= 4,450,611) excluded deaths and non-Michigan births for the period 1974-2005. The Michigan linked data were anonymized and sent to us by the MDCH. We examined the matching on GA and sex, and confirmed the accuracy of these matching procedures. The MDCH also developed lists of cases and controls and separated them into files so that they could be requested by hospitals. Our research team remained masked to any identifying information on study subjects.

Our data cleaning procedure included the following steps:

1) Removing any subject whose BW was less than 500 g or greater than 6,000 g;

2) If GA were less than 20 or greater than 45, then GA was treated as missing;

3) If the difference of GA in case and matched control were greater than 2 weeks, then the control was removed; and

4) If both controls were eliminated, then the corresponding case was also eliminated.

Our final dataset had a total of 2,283 observations (867 cases and 1,416 controls). Most cases had two matched controls, and all cases had at least one matched control. Univariate and multivariate statistical analyses using conditional logistic regression were performed to study association between ALL and perinatal factors of interest. Maximum likelihood estimates of OR, p-value and 95% CI were obtained, taking into account potential confounding factors. Regression analysis in SAS statistical program (version 9.1; SAS Institute Inc., Cary, NC) was used to fit conditional logistic model in this 1:2 matched case–control study. All tests of hypotheses were two-sided at significance level alpha =.05.

To measure FG, we calculated the fetal growth ratio (FGR) by dividing each subject's BW by median BW of the control population for the same gestational week (sample-based denominator). An FGR, which assesses BW in proportion to the mean or median (50th percentile) for GA, can be constructed from any BW-for-GA reference.(225) For the purpose of comparison of results, we also calculated FGRs using US national reference of BW for GA with standards for race and sex as the denominators (population-based denominator). Oken et al had used data from recent nationwide US Natality datasets to generate multiple reference percentiles of BW at each completed week of gestation from 22 through 44 weeks. They analyzed data from 6,690,717 singleton infants with recorded BW and sex born to US resident mothers in 1999 and 2000.(226)

4.3 Results

As shown in Figure 4-1, mean BW was 3,459 g for cases and 3,399 g for controls (mean difference = 59.34 g). Mean duration of gestation was 39.4 weeks in both cases and controls. The ratios of male to female among cases and controls were 1.3 (487/380) and 1.2 (784/632), respectively.

Figure 4-1 Birth weight distribution in ALL cases and matched controls

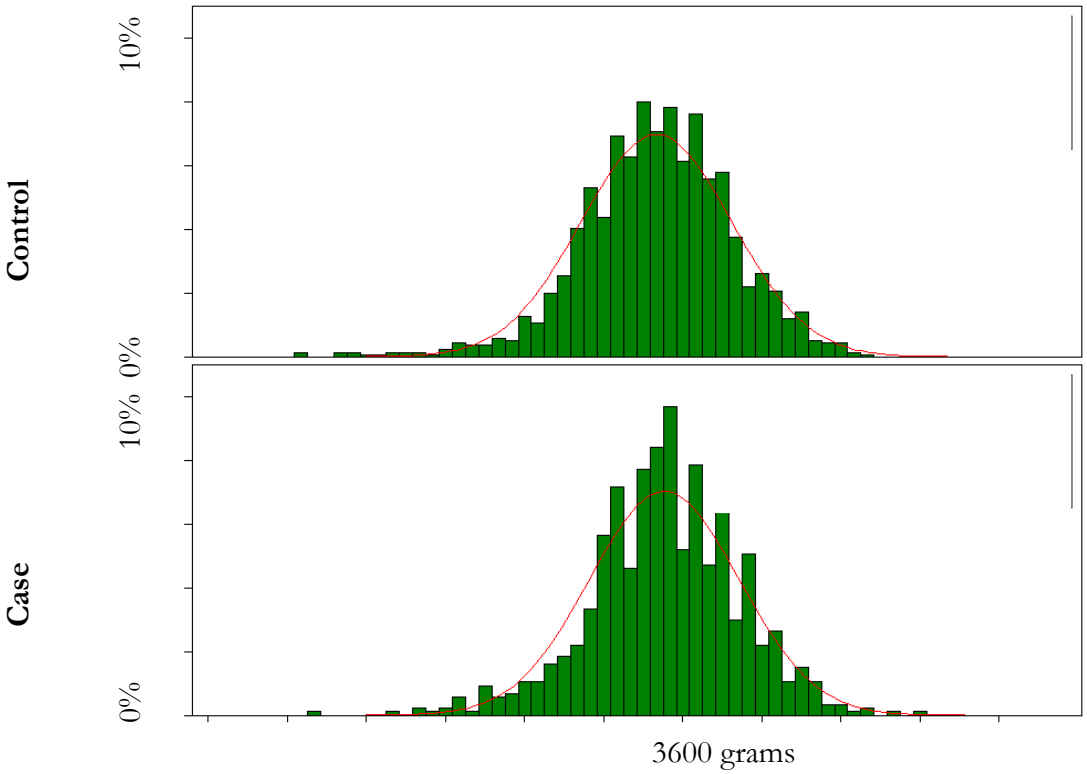


Figure 4-2 shows mean BWs of cases and matched controls in different gestational weeks. When FG was plotted by gestational week, expressed as the FGR (Figure 4-3), cases were fairly consistently larger than controls at all gestational ages after 36 weeks, though at 38 weeks only, the growth difference was negligible. Prior to 36 weeks, the small number of cases and controls in any single week of gestation made for imprecise estimates.

Figure 4-2 Mean birth weights for weeks of gestation in ALL cases and matched controls

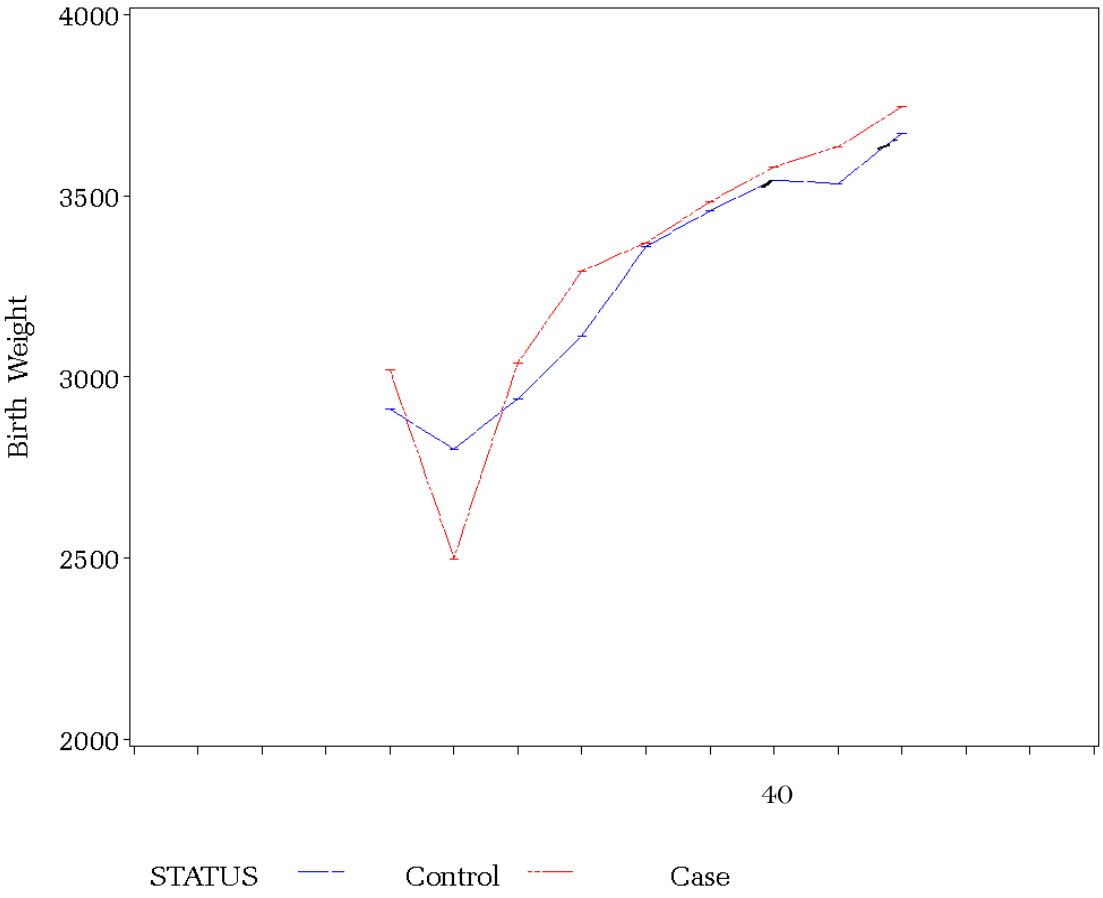
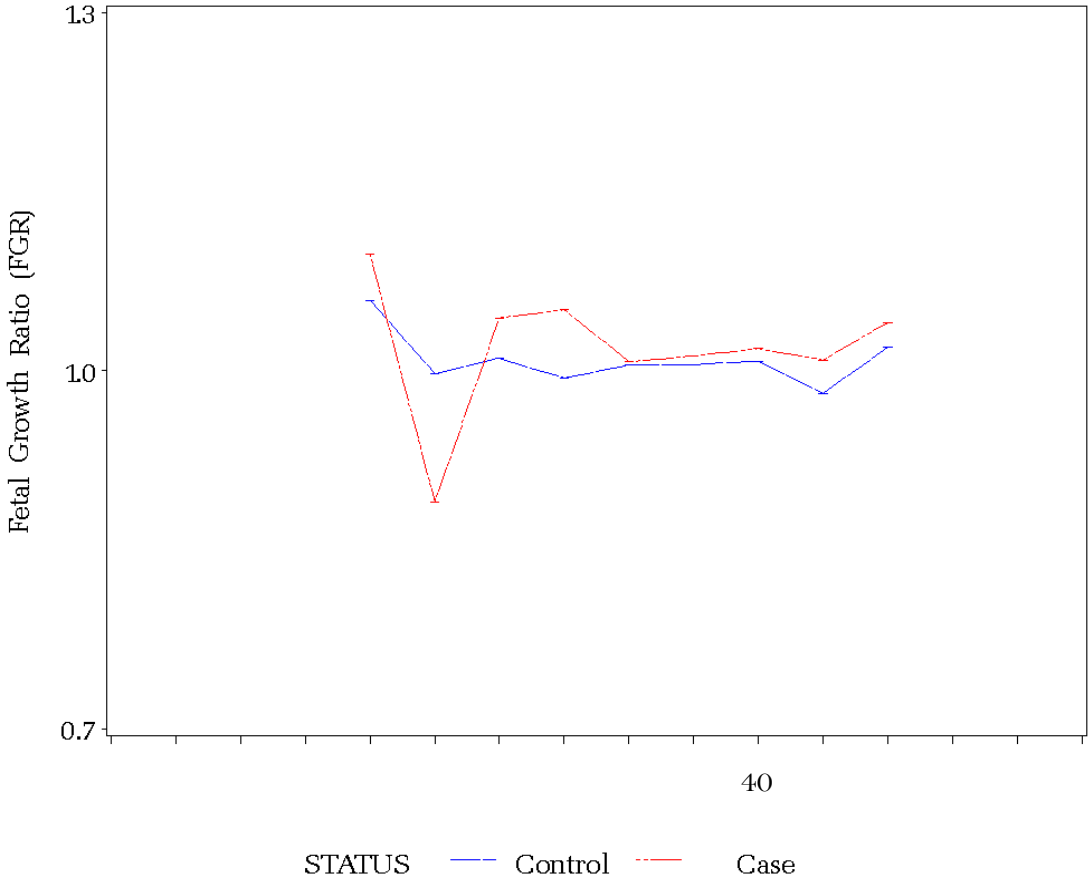


Figure 4-3 Fetal growth ratio (with sample-based denominator) in ALL cases and matched controls, all maternal races combined



Figures 4-4 and 4-5 show mean BWs of cases and controls in each gestational week for white and black maternal races, respectively.

Figure 4-4 Fetal growth ratio (with sample-based denominator) in ALL cases and matched controls, black maternal race

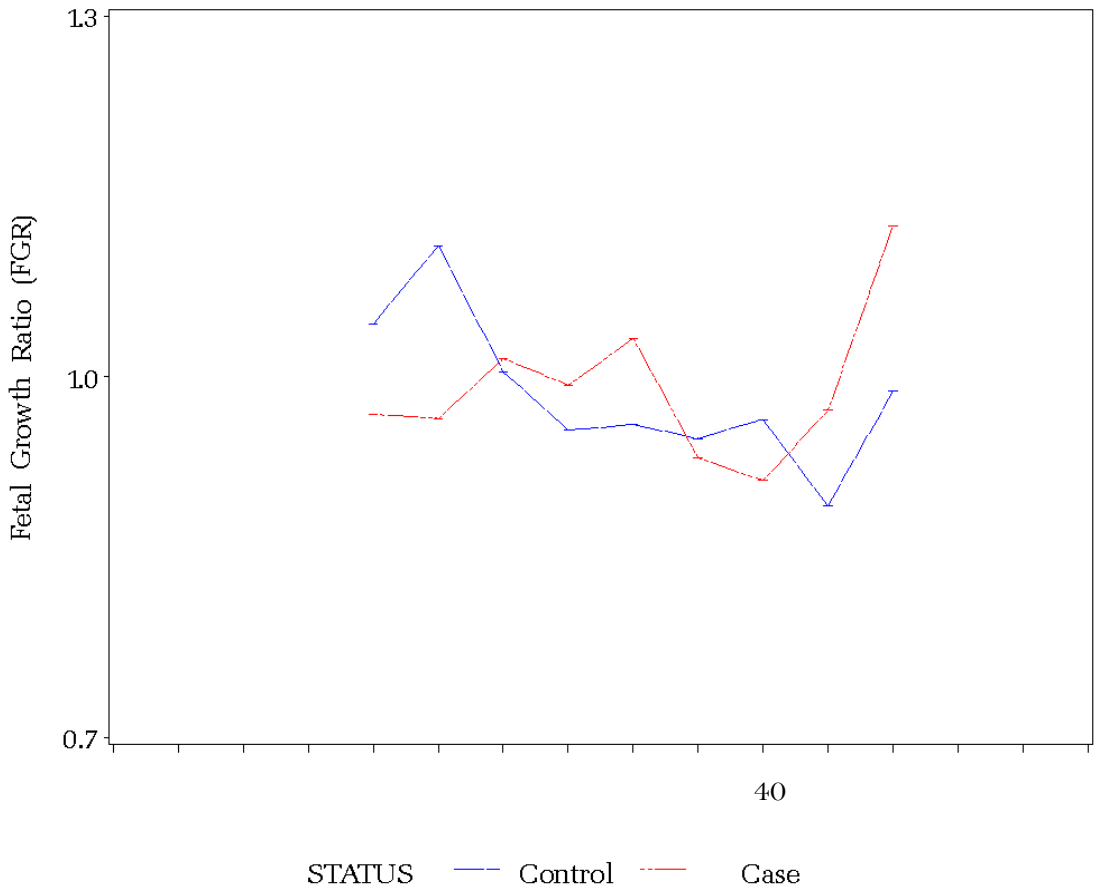


Figure 4-5 Fetal growth ratio (with sample-based denominator) in ALL cases and matched controls, white maternal race

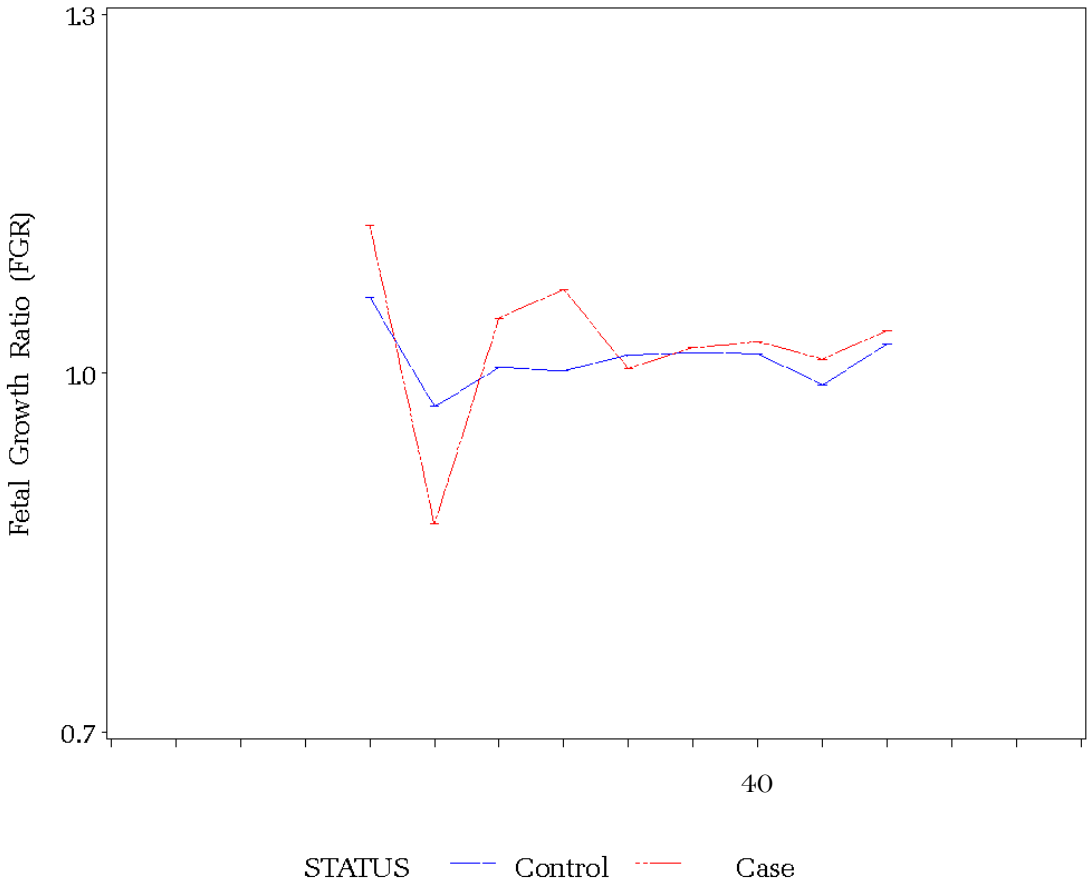


Table 4-1 shows frequencies and crude ORs for select socio-demographic and clinical characteristics of cases and controls. Except for race and maternal age, the characteristics differed very little between cases and controls. The children with white maternal or paternal races had approximately 2.5 times higher risk of ALL [ORs 2.4 (CI 1.7-3.5) and 2.5 (CI 1.6-4.1), respectively]. An increased ALL risk of the same magnitude was measured for the children with North, Central and South American maternal ancestry (OR 2.4, CI 1.2-4.8) or European maternal ancestry (OR 2.6, CI 1.3-5.1). There was also a significant excess risk of

60% for ALL (OR 1.6, CI 1.0-2.4) in the children whose mothers were in the age group 19-45 years.

Maternal education < 17 y was found to have a non-significant protective effect (OR 0.7, CI 0.4-1.0). There was no significant difference in Tobacco and alcohol use among mothers of the cases and matched controls. An almost three-fold non-significant risk of ALL (OR 2.8, CI 0.9-8.8) was measured for the children whose mothers had previous HBW infants. A history of diabetes or lung disease in mothers was not found to be a risk factor for childhood ALL. An interesting finding was that the children who were not admitted to the NICU had a non-significant increased risk of ALL (OR 2.4, CI 0.9-6.3).

Table 4-1 Descriptive characteristics of ALL cases and matched controls

Variable	Category	N Case	% Case	N Control	% Control	OR (a), 95% CI
Socio-Demographic Characteristics:						
Maternal age (y)	0- 18	55	6.34	111	7.84	1
	19- 45	812	93.66	1305	92.16	**1.6 (1.0, 2.4)**
Maternal education (y)	≤ 12	491	61.3	809	62.57	0.7 (0.4, 1.0)
	13- 16	242	30.21	394	30.47	0.7 (0.4, 1.0)
	> 16	68	8.49	90	6.96	1
Maternal race	White	779	89.85	1189	83.97	**2.4 (1.7, 3.5)**
	Black	67	7.73	193	13.63	1
	Unknown	3	0.35	2	0.14	9.4 (0.9, 99.0)
	Others	18	2.08	32	2.26	1.9 (1.0, 3.8)

Table 4-1 (cont'd)

Maternal ancestry	North, Central and South American	187	39.04	294	36.61	**2.4 (1.2, 4.8)**
	European	245	51.15	392	48.82	**2.6 (1.3, 5.1)**
	Asian	23	4.8	36	4.48	2.2 (0.9, 5.3)
	African	24	5.01	81	10.09	1
Paternal race	White	694	80.05	1015	71.68	**2.5 (1.6, 4.1)**
	Black	30	3.46	94	6.64	1
	Unknown	128	14.76	275	19.42	1.6 (1.0, 2.7)
	Others	15	1.73	32	2.26	1.5 (0.7, 3.3)
Tobacco use	Yes	92	18.07	148	17.62	1
	No	407	79.96	672	80	1.2 (0.8, 1.7)
	Blank or unknown	10	1.96	20	2.38	1.1 (0.3, 3.4)
Alcohol use	Yes	13	2.55	18	2.14	1
	No	486	95.48	798	95	1.3 (0.5, 3.4)
	Blank or unknown	10	1.96	24	2.86	0.8 (0.2, 3.3)
Previous infant 4,000+ g	No	855	98.62	1407	99.36	1
	Yes	12	1.38	9	0.64	2.8 (0.9, 8.8)
Diabetes	No	848	97.81	1389	98.09	1
	Yes	19	2.19	27	1.91	0.8 (0.4, 1.6)
Lung disease	No	862	99.42	1409	99.51	1
	Yes	5	0.58	7	0.49	1.2 (0.3, 5.0)
Clinical Characteristics:						
Plurality	Single birth	848	97.81	1384	97.74	1
	Multiple birth	19	2.19	32	2.26	1.1 (0.5, 2.4)

Table 4-1 (cont'd)

Fetal distress	No	850	98.04	1376	97.18	1
	Yes	17	1.96	40	2.82	0.5 (0.3, 1.1)
Vaginal delivery	No	500	57.67	801	56.57	1
	Yes	367	42.33	615	43.43	0.9 (0.7, 1.2)
Primary C-section	No	801	92.39	1301	91.88	1
	Yes	66	7.61	115	8.12	1.0 (0.7, 1.4)
Forceps use	No	857	98.85	1389	98.09	1
	Yes	10	1.15	27	1.91	0.7 (0.3, 1.7)
Vacuum use	No	845	97.46	1387	97.95	1
	Yes	22	2.54	29	2.05	1.1 (0.5, 2.3)
Apgar at 1 min	0 to 3	27	3.11	43	3.04	1.0 (0.4, 2.4)
	4 to 6	62	7.15	95	6.71	1.3 (0.9, 2.0)
	7 to 10	778	89.73	1278	90.25	1
Assisted ventilation	No	849	97.92	1388	98.02	1
	Yes	18	2.08	28	1.98	0.8 (0.3, 1.9)
Assisted Ventilation < 30 min	No	856	98.73	1395	98.52	1
	Yes	11	1.27	21	1.48	0.8 (0.3, 2.1)
Assisted Ventilation >30 min	No	860	99.19	1409	99.51	1
	Yes	7	0.81	7	0.49	0.8 (0.1, 4.5)
NICU admission	Yes	12	2.36	31	3.69	1
	No	487	95.68	799	95.12	2.4 (0.9, 6.3)
	Blank or unknown	10	1.96	10	1.19	20.3 (1.9, 218)

(a) Significant ORs bolded

The clinical characteristics of plurality, fetal distress, method of child delivery, and low Apgar score at 1 minute after birth were not significantly different among cases and controls. Although 2.36% of cases were admitted to the NICU, only 2.08% of cases received assisted ventilation of whom only 7 (out of 18) received assisted ventilation for a total duration of longer than 30 minutes. Overall, the percentages of exposure to assisted ventilation were not significantly different between cases and controls. Nonetheless, these low percentages underline the need to assess hospital records.

Table 4-2 shows frequencies and crude ORs for BW, GA, and FGR. Children who had a BW of 4,000 g or higher had 47% (OR 1.47, CI 1.06-2.03) increased risk of developing ALL compared to their matched controls. Birth weight over 4,000 g was about 4% more common in cases; there was only a very slight difference between cases and controls in the frequency of BW < 2,500 g. Our analysis also showed that for each 1,000 g increase in BW risk of ALL had a significant increase of 21% (OR 1.2, CI 1.0-1.4).

Dividing the samples into quartiles of FG, we found that cases were over-represented most in the highest quartile, over the 75th percentile in growth, but there was no consistent trend across all degrees of FG. Cases were also over-represented in the 2nd quartile of FG, but not in the third. Those with a high (above mean) FGR had 10% excess risk (OR 1.1, CI 1.0-1.4) of ALL which was found to be significant. Further analysis of FGR showed that, compared to low (0-25%) FGR group, the high (75-100%) FGR group had over 50% higher (OR 1.52, CI 1.1-2.1) risk of developing ALL.

Table 4-2 Frequencies and odds ratios of birth weight, gestational age, fetal growth, and risk of ALL

Variable	Category	N Case	% Case	N Control	% Control	OR (a), 95% CI
Birth weight (g)	< 2,500	47	5.42	80	5.65	1.11 (0.61, 2.03)
	2,500-3,999	683	78.78	1167	82.42	1
	≥ 4,000	137	15.8	169	11.94	**1.47 (1.06, 2.03)**
Gestational age (w)	< 35	31	3.58	47	3.32	
	35- 37	97	11.19	162	11.44	
	38- 41	672	77.51	1089	76.91	
	≥ 42	67	7.73	118	8.33	
FGR (2 categories)	Low 50%	413	47.64	722	50.99	1
	High 50%	454	52.36	694	49.01	**1.1 (1.0, 1.4)**
FGR (4 categories)	0-25%	187	21.57	377	26.62	1
	25-50%	226	26.07	345	24.36	1.29 (0.93, 1.78)
	50-75%	211	24.34	372	26.27	0.98 (0.70, 1.38)
	75-100%	243	28.03	322	22.74	**1.52 (1.10, 2.10)**

(a) Significant ORs bolded

Table 4-3 shows crude ORs for the FGRs (categorical, continuous) with sample- and population-based denominators. For each unit increase of FGR, odds of developing ALL increases significantly (OR 1.77, CI 1.07-2.92), if an FGR with sample-based denominator is taken into consideration.

Table 4-3 Crude odds ratios of FGRs (with sample-based, and population-based denominators), and risk of ALL

FGR Category	Sample-Based FGR OR (95% CI) *	Population-Based FGR OR (95% CI) (a)
25-75% vs 0-25%	1.20 (0.97, 1.48)	1.18 (0.95, 1.48)
75-100% vs 0-25%	**1.51** (1.18, 1.93)	**1.40** (1.08, 1.80)
per 1 unit	**1.77** (1.07, 2.92)	1.57 (0.95, 2.58)

(a) Significant ORs bolded

Table 4-4 shows a significant excess risk of 48% for high FGR category, compared to low FGR, after adjusting for maternal race. In this multivariate model, the variable FGR has a significant p-value (0.0064).

Table 4-4 Adjusted odds ratios for FGR (with sample-based denominator), maternal race, and risk of ALL

	OR Estimate (a)			p-value
Variable	**Point Estimate**	**95% Wald Confidence Limit**		
FGR: 25-75% vs 0-25% (ref)	1.15	0.93	1.43	0.0064
FGR: 75-100% vs 0-25%	**1.48**	1.16	1.91	
Maternal race: White vs Black (ref)	**2.35**	1.63	3.38	<.0001
Maternal race: Other vs Black	1.96	0.79	4.85	

(a) Adjusted for other variable listed in the table; significant ORs bolded

Table 4-5 shows a significant excess risk of 33% for HBW category, compared to NBW, after adjusting for maternal race. However, the variable BW is not significant in this model (p-value= 0.0913).

Table 4-5 Adjusted odds ratios for birth weight, maternal race, and risk of ALL

	OR Estimate (a)			p-value
Variable	**Point Estimate**	**95% Wald Confidence Limit**		
BW: 4,000-6,000 vs 2,500-3,999 (g; ref)	**1.33**	1.03	1.71	0.0913
BW: 500-2,499 vs 2,500-3,999	1.02	0.66	1.59	
Maternal race: White vs Black (ref)	**2.38**	1.65	3.43	<.0001
Maternal race: Other vs Black	1.91	0.78	4.69	

(a) Adjusted for other variable listed in the table; significant ORs bolded

Table 4-6 shows parameter estimates for a multivariate model including the interaction term, BW-maternal smoking. Based on this model, there is a significant excess risk of over 2.5 times among HBW babies whose mothers smoke during pregnancy (OR 2.58, CI 1.11-5.99). The risk of ALL in HBW babies with non-smoker mothers is significantly less than two fold (OR 1.81, CI 1.15-2.86).

Table 4-6 Adjusted odds ratios for birth weight, maternal race, maternal smoking, and risk of ALL

	OR Estimate (a)			p-value
Variable	**Point Estimate**	**95% Wald Confidence Limit**		
BW: 4,000-6,000 vs 2,500-3,999 (g; ref) if smoker	**2.58**	1.11	5.99	0.0209 (b)
BW: 500-2,499 vs 2,500-3,999 if smoker	0.87	0.38	2.02	
BW: 4,000-6,000 vs 2,500-3,999 if non-smoker	**1.81**	1.15	2.86	
BW: 500-2,499 vs 2,500-3,999 if non-smoker	0.82	0.49	1.35	
Maternal race: White vs Black (ref)	**3.12**	1.84	5.26	0.0001
Maternal race: Other vs Black	**3.54**	1.13	11.04	

(a) Adjusted for other variable listed in the table; significant ORs bolded
(b) P-value for interaction term (interaction between BW and maternal smoking)

4.4 Discussion

Our study shows a markedly increased risk of ALL associated with HBW, parental white race, and maternal age > 18 y. These results are consistent with the findings of many other studies.

4.4.1 Birth weight

Among epidemiological studies of environmental, lifestyle, and reproductive factors, the most consistent risk factor for ALL (outside of in-utero radiation exposure) is HBW.(227) Our (two-phase) study has confirmed the higher BWs of leukemic infants in our entire sample (and in the subset for whom we abstracted hospital records).

The literature is consistent in finding that HBW is linked to ALL.(68) (71) (228) (229) (219, 230) A meta-analysis of 18 studies of the association between BW and ALL showed a 30% excess of ALL (OR 1.3, 95% CI 1.2-1.4) in children who had weighed 4,000 g or more at birth as well as a dose-response relationship for BW (OR 1.14 for each 1,000 g increase, CI 1.08-1.20).(231) According to a very recent British study, the risk for overall leukemia increases 7% with each 0.5 kg increase in BW (OR 1.07, 95% CI 1.04-1.10). Analysis by cytogenetic feature reveals that there appears to be association with specific chromosomal abnormality.(232)

The combined available evidence from observational studies suggests that HBW is associated with an increased risk of overall leukemia (OL) and ALL; for AML, the risk may be elevated at both high and low extremes of BW, suggesting a U-shaped association. Caughey and Michels conducted a fixed effect meta-analysis of 32 studies including 16,501 cases of OL, 10,974 cases of ALL, and 1,832 cases of AML. The ORs for the association of HBW with OL and ALL were 1.35 (95% CI 1.24-1.48) and 1.23 (CI 1.15-1.32), respectively. The OR for OL was 1.18 (CI 1.13-1.23) and for ALL 1.18 (CI 1.12-1.23) per 1,000 g increase in BW.(59) Interestingly, a medical record-based study of leukemia and non-Hodgkin's lymphoma diagnosed before the age of 30 years carried out at three hospitals in the south of

England (177 cases, 354 age- and sex-matched controls) showed the preceding siblings of those diagnosed with any form of leukemia were also more likely to weigh > 3,500 g at birth (OR 2.2; 95% CI 1.1-4.4).(60) A Brazilian study of childhood cancers showed that, after adjusting for GA, the BW of 4,000 g or more was associated with a statistically significantly higher risk of risk of leukemia.(233)

4.4.2 Gestational age

Relation between GA and ALL is a matter of controversy.(234) In a multi-country Scandinavian study significantly reduced risks of B-precursor ALL were observed with increasing GA (OR 0.87 per 2-week increase in GA, 95% CI 0.81-0.94).(61) Based on our study design, we were well able to match study controls on GA rather than control for it through multivariate analyses.

Although there is some argument against the idea of adjustment for GA,(214) there are studies which have proposed that BW corrected for GA is a better predictor than BW alone of risk for ALL.(70) (215) A very recent California study (ALL n= 4,721) showed that GA adjusted for BW, birth order, mother's age, father's education, child's race, and payment source for delivery when entered in the model as a continuous variable with 1-week and 2-week increments had an OR of 0.97 (CI 0.95-1.00) and an OR of 0.95 (CI 0.90-1.00), respectively. Gestational age entered into the model as a categorical variable gave similar results.(235)

4.4.3 Fetal growth

Previous studies have found that HBW is associated with risk of ALL but have not generally examined this relationship in more detail. We have found that:

a) The association of BW with leukemia is based entirely on FG;
b) Birth weight over 4,000 g is substantially over-represented in children who subsequently develop ALL;
c) Fetal size for GA, however assessed, is larger for children who develop ALL than controls at all gestational ages from 37-41 weeks, except possibly at 38 weeks; and
d) The quartile of FG that places children most at risk for ALL is the highest quartile, above the 75th percentile. Below that threshold, correlations with ALL are inconsistent.

Our FG findings are broadly consistent with some studies that have also attempted to examine BW more closely in children with ALL. A 2006 study in New York State suggested that childhood leukemia might be related to factors influencing abnormal FG patterns. For ALL, there was evidence of effect modification with BW and maternal pre-pregnancy weight. High BW was associated with ALL only when the mother was not overweight while heavier maternal weight was associated with ALL only when the infant was not HBW.(236)

A 2007 Australian study showed a moderately strong, positive association between risk of ALL and proportion of optimal birth weight (POBW) using linked medical records. The HR for a 1-standard-deviation (SD) increase in POBW was 1.25 (95% CI: 1.07-1.47). Among children younger than 5 years not classified as having HBW (defined as >3,500 g, >3,800 g, and >4,000 g), a 1-unit increase in POBW was associated with an approximately

40% increase in ALL risk.(223) The Australian Study of Causes of ALL in Children (347 cases and 762 controls aged <15 years) confirmed the earlier findings; the OR for a 1-SD increase in POBW was 1.18 (CI 1.04-1.35) after adjustment for potential confounders.(222) This study was the first to investigate the association between FG and ALL by disease subtype.

Of note, the Jerusalem Perinatal Study showed that having delivered a baby of BW > 4,500 g in any pregnancy increased a woman's risk of leukemia three-fold. No such risk was seen in fathers of large babies.(237) Thus, the linkage between FG and leukemia may have genetic links, or pregnancy processes, possibly hormonal, may affect leukemia risk of both the mother and the fetus. In fact, a recent Danish study showed that prevalence and quantity of pre-leukemic t(12;21)-positive cells peaks at term or early childhood.(238) A very recent pooled analysis of case-control data from Germany, UK and US (4,075 ALL cases and 12,065 controls) found that children with ALL were, on average, heavier than controls at all gestations, the disparity being driven by a deficit of LBW at all gestations and an excess of HBW at 40 weeks.(62)

In summary, recent studies suggest that accelerated FG is associated with increased risk of childhood leukemia.(222, 223, 227, 239) Evidence is also gathering that certain dietary intakes, possibly folate, in mothers, are also related to leukemia occurrence.(123, 240) Genetic variation in methionine synthase could mediate risk of childhood leukemia, either via effects on DNA methylation or via effects on FG and development.(241) If these associations are real, they may be operating through GF pathways.(242) The levels of GFs and hormones are strongly associated with stem cell potential in human umbilical cord

blood.(243) The biological mechanism behind the association between HBW and childhood leukemia may involve IGF-I.(244-247) The GF may act by increasing the absolute number of stem cells available for transformation, stimulating the growth of cells that are already transformed, or a combination of effects.(63) The potential underlying biological mechanisms linking the IGF system with the development of specific childhood cancers have not been elucidated.(248) Interestingly, the documentation of higher cord blood levels of IGF-1, a principal GH that does not cross the placenta, among Caucasian than in Asian newborns is concordant with higher incidence of certain cancers (e.g., breast cancer) in these populations.(249)

The relative simplicity of tumor genetics of common subtypes of leukemia and the availability of archived material in the form of archived neonatal blood spots (ANBs or Guthrie cards) has permitted the tracing of many genetic events to fetal origins using sensitive amplification methods.(250) A 2012 study was the first to identify an association between the genes involved in the IGF axis and risk of childhood ALL. These findings emphasize the importance of FG, when lymphoid progenitor cells are not yet fully differentiated and therefore more susceptible to malignant transformation.(224) Children with ALL may also have a dysregulated immune function present at birth.(251)

4.4.4 Race

Our analysis of data available on birth certificates shows a markedly reduced risk for black infants. The effect of black race has also been confirmed using hospital data (Phase II of our study). A number of studies conducted in the US show that black race has a protective

effect on the development of ALL.(71) (68) (70) (33) For the period 1997-2002, Hispanics in the US had a higher incidence of ALL, particularly in childhood, and promyelocytic leukemia than did non-Hispanics.(30)

A Texas study shows that the association between race/ethnicity and childhood cancer is independent of BW and, conversely, that adjustment for race/ ethnicity has little impact on estimated effects of HBW.(252) In our study, after adjustment for maternal race, the OR of HBW dropped only about 10% (from 1.47 to 1.33) and remained significant. However, as mentioned earlier, overall, the BW variable was not significant in this model (p-value= 0.0913).

The protective effect of black race might be related to the level of melatonin, a ubiquitously acting free radical scavenger. Findings of a recent study indicate that melatonin is a potential physiological tool capable of protecting healthy cells from chemotherapy-induced ROS production as well as inducing tumor cell death.(253)

4.4.5 Maternal age

Our study shows that there is significant association between maternal age > 18 years and ALL. The second phase of our study also showed a significant association between high maternal age and ALL. This is consistent with the findings of several other studies.(67) (68) (69) (70) (71) Interestingly, a recent study in California found that children with paternal age between 35 and 45 years (compared to < 25) were at increased risk of total childhood leukemia (OR 1.12; 95% CI 1.04-1.40) and ALL (OR 1.23; CI 1.04-1.47).(235)

A Swedish study showed that childhood leukemia risk increased with maternal age for mothers born in the past, whereas maternal age had no effect on this risk for mothers born more recently. This finding suggests that leukemia risk may be related to an environmental factor to which women's exposure has changed over time.(213) It might be possible to relate high maternal age and parity to oxidative stress. Mutlu et al suggest a relation between higher maternal parity and increased oxidative stress and decreased antioxidant defense capacity. However, the compensatory mechanisms improve the antioxidant defense system in newborns of grand multiparous women and may prevent oxidative stress.(254)

There is also strong evidence that maternal age has significant association with DS.(72, 255) Down syndrome is the most common chromosomal abnormality in children and also carries a marked increased incidence of acute leukemia.(256-258) Several studies have shown significant association between DS and ALL.(71, 161, 230) For the purpose of our study, we did not exclude the observations with DS due to very low proportion of the study subjects who had DS.

4.4.6 Smoking and alcohol

Our study did not show any significant association between maternal smoking, alcohol consumption and ALL. However, after the inclusion of smoking as an interaction term in a multivariate model, the OR for HBW and smoking (controlling for maternal race) was significantly high (2.6, CI 1.1-5.9). Based on this model, if non-smoker, the (race-) adjusted OR for HBW was below 2 (1.8, CI 1.1-2.9). This is clearly an indication of the effect modification role maternal smoking plays on the pathway between BW and ALL.

It is an established fact that smoking, history of preterm delivery, and hypertensive diseases in the current pregnancy all have negative effects on BW, whereas babies of diabetic mothers weigh more.(259) Although tobacco smoke is an established risk factor for adult myeloid leukemia, the studies of association between parental smoking and childhood leukemia have produced inconsistent results. The majority of the studies on maternal smoking and childhood leukemia did not find a significant positive association and some even reported an inverse association.(83) In contrast to studies of maternal smoking, studies of paternal smoking and childhood leukemia reported more positive associations but only by less than half of the studies.(82)

Inconsistencies in the results and the low risks reported do not suggest an association between childhood cancer and parental consumption of alcohol.(126) The Cross-Canada Childhood Leukemia Study showed that maternal alcohol consumption prior to conception (OR 1.37, 95% CI 0.99-1.90) and during pregnancy (OR 1.39, CI 1.01-1.93) was associated with an excess risk of childhood leukemia, with a positive dose-response trend for increasing weekly consumption ($p < 0.05$). Similar results were observed for children diagnosed with ALL. In this study, ORs for maternal cigarette smoking before and during pregnancy were consistently elevated above one, but not statistically significant. No relationship was observed with paternal drinking or smoking in the perinatal period.(260)

4.4.7 Apgar score and assisted ventilation

Additional findings from our analysis of the data available on birth certificates show no excess risk for infants with low Apgar scores or assisted ventilation, both possible markers of

oxygen exposure. Indeed, our two-phase study was stimulated by reports that oxygen exposure might increase the risk of leukemia.(162, 163) Our study showed that requirement for assisted ventilation, the only birth certificate variable that is directly related to oxygen supplementation, was recorded in only 2% of live births. A study of ALL in Minnesota, did not find any association between assisted ventilation and ALL either.(68) However, in a large cohort study in the US, the HR for all childhood cancers was 2.9 (95% CI 1.5-5.7) with exposure to 3 or more minutes of oxygen.(163) The results of Spector's study are consistent with those reported by Naumburg et al in Sweden.(162)

4.4.8 Strengths

Despite the rarity of childhood cancers, we could obtain a relatively large sample of cases in the State of Michigan. However, general limitations of case-control studies apply to our study, but the most important limitation, recall bias, did not operate, as our exposure information was collected years prior to the diagnosis. In addition, we believe our relatively diverse and representative study population has several merits.

Slusky et al underlines that, in interview-based case-control studies of childhood cancer, the proportion of whites compared to non-whites tends to be higher among controls than among cases; however, the opposite is true for record-based case-control studies.(261) Our study population came from all over the state (minimal selection bias); we later conducted hospital record review in identical fashion for cases and controls (phase II), and verified a considerable part of our state-level data through comparison with hospital data (minimal information bias).

The major strength of our study is its design which includes a two-phase approach allowing us to obtain a matched control sample in the first phase, and to collect detailed information on neonatal and maternal exposures (from medical records) in the second phase, providing high internal validity to our study. Since additional resources (multiple funding) became available, we were able to obtain linked data on all cases of ALL diagnosed at under 10 years of age in Michigan to reach an optimal sample size.

We had two strategies for addressing confounding should it occur. First, we matched our controls to cases. The main matching criterion is GA. Likewise, all controls were born in the same hospitals as cases at about the same time, so that differences in practice patterns across hospitals and over time are not confounding. We could also adjust in the analysis of our data for any potential confounder. Although case-control studies generally have more cases and therefore higher statistical power than cohort studies, they are more prone to reporting or recall bias, which can occur if parents of cases classify exposure differently than do control parents.(98) Our study did not involve any parental self-report or interview (which could introduce recall bias).

4.4.9 Limitations

The population-based, state-wide selection of cases and comparable controls suggests that selection bias is unlikely to account for the exposure-outcome associations of interest. Furthermore, exposure data were obtained retrospectively in a standardized fashion for virtually all births. Although some exposures might have been underreported, this underreporting should not differ between cases and controls but would reduce statistical

power to detect any effects. Data on various exposures such as smoking are usually recorded poorly unless they are collected in an obligatory manner as part of the routine admissions data collection process.(217)

4.5 Implications

Our study highlights the importance of accelerated FG as a possible risk factor of ALL and maternal smoking as an effect modifier. High FG above the 75th percentile measured during weeks 37-41 weeks might be a clinical warning sign for ALL, the most common childhood malignancy. This should be taken into serious consideration if the pregnant woman is white and smoker. Multi-state studies with very large sample size can provide more details on this important topic.

Chapter 5: FUTURE DIRECTIONS OF EPIDEMIOLOGICAL RESEARCH ON ACUTE LYMPHOCYTIC LEUKEMIA

Epidemiologic studies of childhood cancer require a considerably large sample size and uniform data collection standards in order for researchers to obtain reliable and generalizeable results. Adequate caution should be taken in the interpretation of risks reliant on self-reported occupational data.(262) Use of data from population-based cancer registries supplemented by linkage with administrative databases, along with new developments in medical informatics and electronic medical records, may facilitate monitoring of the translation of basic science and clinical advances to cancer prevention, detection, and uniformly high quality of care in all areas and populations.(263)

The following sections provide some discussion on certain factors which merit further scientific investigation. Future direction should focus on the identification of biologic factors that predict significantly poorer outcomes so that new targeted approaches may be investigated.(264)

5.1 Oxygen

5.1.1 Hypoxia Paradox

Hypoxia is a critical stimulus which switches on a cell rapid response, determining damage and death in some cells, and adaptation and survival in others. Di Giacomo et al suggest a dual role for Hypoxia Inducible Factor (HIF)-1alpha in providing a survival or death signal,

based on hypoxia duration, and consider the nuclear transcription factor, CREB (c-AMP Response Element Binding) protein, to be a possible target for hypoxic therapy against leukemia.(265) Another study suggests that hypoxia-induced in vitro differentiation of mouse embryonic stem cells (mESCs) is triggered, at least in part, by the HIF-1alpha-mediated suppression of leukemia inhibitory factor (LIF)-STAT3 signaling.(266)

Hypoxia-inducible factor 1 (HIF-1) is the key transcription factor regulating hypoxia-dependent gene expression. Lack of oxygen stabilizes HIF-1, which in turn modulates the gene expression pattern to adapt cells to the hypoxic environment. Activation of HIF-1 is also detected in most solid tumors and supports tumor growth through the expression of target genes that are involved in processes like cell proliferation, energy metabolism, and oxygen delivery.(267)

Leukemia inhibitory factor (LIF) promotes survival of glial cells and neurons during autoimmune and injury responses in the central nervous system (CNS). This factor inhibits the production of oxygen radicals and TNFalpha and stimulates myelin uptake by macrophages. These effects of LIF are accompanied by activation of the JAK/STAT3 signalling pathway.(268) Tissues and advancing vasculature communicate to ensure adequate vascularization using LIF as well as oxygen, which suggests a new strategy for antiangiogenic therapy in human diseases such as diabetic retinopathy and cancer.(269) Increased LIF expression in peri-infarcted regions and sequestration from the peripheral circulation in acute stroke patients are characteristic of the pathobiological response to ischemia and tissue damage.(270)

Undifferentiated embryonic stem (ES) cells adapt their energy metabolism to proliferate at all oxygen partial pressure (pO_2) between 0 and 285 mmHg. Oxygen has minimal effects on undifferentiated cell growth and phenotype, but may exert more substantial effects under differentiating conditions.(145)

5.1.2 ROS

The compounds bearing o-diphenoxyl groups exhibit remarkably higher activities in inhibiting ROS-induced DNA damage, accelerating DNA damage in the presence of cupric ions, and inducing apoptosis of HL-60 cells compared with the ones bearing no such groups.(271) Vitamin C is an antioxidant vitamin that has been hypothesized to antagonize the effects of ROS-generating antineoplastic drugs.(272) As a reducing agent, ascorbate serves as an antioxidant. However, its reducing function can in some settings initiate an oxidation cascade, i.e., seem to be a "pro-oxidant." This dichotomy also seems to hold when ascorbate is present during photosensitization.(273)

Radiation-induced apoptosis in MOLT-4 cells requires elevation of intracellular ROS as well as activation of a series of caspases, whereas the cryptic necrosis program--which is independent of intracellular ROS generation and caspase activation--is activated when the apoptosis pathway is blocked.(274)

Leukemia, blood disorders, bone marrow depression, and some types of cancer are directly related to benzene-initiated toxicity. Bioactivation of benzene can lead to the formation of hazardous metabolites such as phenol, hydroquinone, and catechol. Catechol forms

semiquinones and reactive quinones that are presumed to play an important role in the generation of ROS.(275) It is hypothesized that the increasing incidence of childhood leukemia may be due to in utero exposure to environmental pollutants such as benzene, but the mechanisms involved remain unknown. A study suggests that ROS play a key role in the development of in utero-initiated benzene toxicity potentially through disruption of hematopoietic cell signaling pathways.(276)

The higher oxidative stress of children with ALL is associated with the protocol for treating ALL which is much more aggressive and frequent than that of the solid tumors. The lower antioxidant status in plasma with ALL children is probably associated with increased ROS as indicated by the decrease of the antioxidant activity. This oxidative stress may lead to cell death or greater sensitivity of the tumor cell to therapy, with better outcome for pediatric patients with ALL.(153) Ionizing irradiation leads to a persistent decline in the numbers and fitness of hematopoietic stem cells, in part resulting from persistent induction of ROS.(277) The discovery of superoxide-generating enzymes homologues of phagocytic NAD(P)H oxidase, the Nox family, has led to the concept that ROS are intentionally generated with biological functions in various cell types. By treating an acute leukemic cell line with different antioxidants, ROS generation was shown to be crucially involved in the modulation of glucose transport (mediated by Glut1), which is frequently up-regulated in cancer cells.(278)

Long-term self-renewing hematopoietic stem cells (HSCs) normally possess low levels of intracellular ROS. However, when intracellular ROS levels become excessive, they cause senescence or apoptosis, resulting in a failure of HSC self-renewal. The repression of

intracellular ROS levels in HSCs by treatment with an antioxidant that scavenges ROS can rescue HSC functions, indicating that excess ROS levels are at the root of HSC failure. Further investigations on the molecular mechanisms of ROS regulation and on the manipulation of excess ROS levels could lead to the development of novel therapeutics for hematopoietic diseases, regenerative medicine, and the prevention of leukemia.(158)

5.2 Genetic factors

High hyperdiploidy (51-67 chromosomes) is the most common cytogenetic abnormality pattern in childhood B-cell precursor ALL, occurring in 25-30% of such cases. High hyperdiploid ALL is characterized cytogenetically by a nonrandom gain of chromosomes X, 4, 6, 10, 14, 17, 18, and 21 and clinically by a favorable prognosis. Despite the high frequency of this karyotypic subgroup, many questions remain regarding the epidemiology, etiology, presence of other genetic changes, the time and cell of origin, and the formation and pathogenetic consequences of high hyperdiploidy.(279)

Chromosomal translocation breakpoints in ALL are among those that define regions of the genome of oncogenic potential, the recognition of which has led to an improved understanding of the mechanisms of leukemogenesis.(280) Leukemogenesis in children may be associated with genetic variants and that the combination of genotypes seems to be more predictive of risk than either of them independently.(281) Apart from showing that leukemias segregate according to lineage and genetic subtype, Andersson et al conducted an extensive study of the genes correlating with primary genetic changes.(282) Global gene

expression profiling provides a valuable tool for genetic and clinical classification of childhood leukemias. (283)

The investigation of a single enzyme and/or a single genotype might not be sufficient to explain the etiology of childhood leukemia because of the complexity of the environment and that of the inter-individual variability in cancer susceptibility.(284) For instance, a study by Yang et al suggests a possible association between electric transformers and power lines and the XRCC1 Ex9+16A allele in patients with childhood sporadic acute leukemia.(285)

Future activities will be aimed at (i) defining the genetic variables that affect micronucleus (MN) frequencies, (ii) validation of various automated scoring systems based on image analysis, flow cytometry and laser scanning cytometry, (iii) standardisation of protocols for scoring micronuclei (MNi) in cells from other tissues, e.g., erythrocyte and nasal cells, and (iv) prospective association studies with pregnancy complications, developmental defects, childhood cancers, cardiovascular disease and neurodegenerative diseases.(286)

Examining leukemogenesis in DS children may identify factors linked to the general development of childhood leukemia and lead to potential new therapeutic strategies to fight this disease.(73) Children of mixed ancestry tend to have disease risks that are more similar to those of racial/ethnic minority children than the white majority group. This tendency may help formulate etiologic studies designed to study possible genetic and environmental differences more directly.(33)

A genome-wide association study in Korean children identified a few genetic variations as potential susceptibility markers for ALL, warranting further replication studies among various ethnic groups.(287) Genetic polymorphisms in innate immunity genes might play a role in the genesis of childhood leukemia with limited biologic evidence. Additional, larger studies are needed to identify the mechanism of these genes in childhood leukemia patients.(288)

In addition to the best study design possible, it may be wise to focus on biomarkers of exposure that could be exploited from currently available resources as well as to incorporate gene–environment interaction when feasible.(18) Various approaches with advanced technologies, e.g., genomics, exposomics, have accelerated development of new biomarkers for biological monitoring of occupational and environmental carcinogens. These advanced approaches are promising to improve quality of life and to prevent occupational and environmental cancers.(289) Some researchers are exploring the use of proteomics to subclassify leukemia, because cytogenetic analysis is costly and time-consuming. Several proteins have been identified that may serve as useful biomarkers for rapidly identifying different forms of childhood leukemia.(240)

5.3 Gene- oxygen interaction

The two most common genetic subgroups of pediatric B-cell precursor ALL are the ones represented by t(12;21)(p13;q22), leading to the EVT6/RUNX1 fusion, or high hyperdiploidy.(290) Although these genetic aberrations most likely are of utmost importance for leukemogenesis, there is ample evidence that they are not sufficient for

leukemic transformation.(291) The strongest support in favor of this has come from studies identifying ETV6/RUNX1 or high hyperdiploidy in neonatal blood spots from children who later developed ALL. Thus, these changes occur prenatally but secondary events are needed for overt disease. Gene dysregulation through hypermethylation may be such an event.(292) Roman-Gomez et al reported that gene methylation in ALL cells was the most important way to inactivate cancer-related genes in this disease. In fact, this epigenetic event can help to inactivate tumor-suppressive apoptotic or growth-arresting responses and has prognostic impact in B- and T-ALL. The presence in individual tumors of multiple genes simultaneously methylated is an independent factor of poor prognosis in both childhood and adult ALL in terms of disease-free survival and overall survival. Moreover, methylation status is able to redefine the prognosis of selected ALL groups with well-established prognostic features.(293)

The ability of chemotherapeutic drugs to inhibit DNA methylation and thereby activate previously silent genes may enable them to promote the aggressiveness of cancers in vivo, including the expression of drug resistance.(294) Epigenetic lesions, e.g., promoter silencing by hypermethylation of the p15/INK4b and other genes, are also increasingly recognized as important in the pathogenesis of acute myeloid leukemia (AML). (295)

Environmental carcinogens contained in air pollution, such as polycyclic aromatic hydrocarbons, aromatic amines or N-nitroso compounds, predominantly form DNA adducts but can also generate interstrand cross-links and ROS. If unrepaired, such lesions increase the risk of somatic mutations and cancer. Further investigations of the combined

effects of polymorphisms within these DNA repair genes, smoking and other risk factors may help to clarify the influence of genetic variation in the carcinogenic process.(296)

5.4 Maternal Smoking

Although tobacco smoke is an established risk factor for AML, the studies of association between parental smoking and childhood leukemia have produced inconsistent results. As mentioned earlier, the majority of the studies on maternal smoking and childhood leukemia did not find a significant positive association and some even reported an inverse association. In contrast to studies of maternal smoking, studies of paternal smoking and childhood leukemia reported more positive associations but only by less than half of the studies. Future directions to be considered for improving the study of parental smoking and childhood leukemia are: 1) consider all sources of benzene exposure including occupational exposure and traffic exhausts; 2) grouping childhood leukemia into more homogeneous groups by molecular techniques; and 3) assess gene-environment interaction.(82)

Buico et al compared the plasma of untreated patients with leukemia/solid gynecological tumors (n = 50) and current regular smokers (n = 50) with a smoking history of >or=10 cigarettes per day to the plasma of healthy blood donors. Standard tools were used to measure total oxidant status, ceruloplasmin activity, total antioxidant capacity, uric acid content and oxidative stress index. Statistically significant differences between the smokers and the control group were detected for all of the biochemical parameters. Conversely, the differences in the cancer patients were not statistically significant for oxidative stress.(297)

Cigarette smoke-mediated oxidative stress induces an inflammatory response in the lungs by stimulating the release of proinflammatory cytokines. Chromatin remodeling due to histone acetylation and deacetylation is known to play an important role in transcriptional regulation of proinflammatory genes. Cigarette smoke-induced release of IL-8 is associated with activation of NF-kappaB via IKK and reduction in HDAC levels/activity in macrophages. Moreover, cigarette smoke-mediated proinflammatory events are regulated by the redox status of the cells.(298) Nicotine enhances newborn piglets' ability to endure hypoxia, and resuscitation with 21% oxygen inflicts less necrosis than 100% oxygen.(299)

5.5 Infectious factors

Hypotheses of an infectious etiology (e.g., hygiene hypothesis) have been around for a long time. One of these involves the possibility of a specific infectious agent having a causative role. Another theory relates to the possible involvement of unusual patterns of infections in infancy and how they might relate to aberrant immune responses.(42) The Northern California Childhood Leukemia Study showed that, in non-Hispanic White children, children in the highest category of total child-hours of exposure to day care have a reduced risk of ALL, particularly common B-cell precursor ALL (c-ALL), compared with children without such exposures, with evidence of a dose-response effect.(51) Less than 10% of the global incidence of leukemias and lymphomas can be linked to documented specific infections (Epstein-Barr virus, human T-lymphotropic retrovirus, human herpesvirus type 8 and Helicobacter pylori). A hypothesis by zur Hausen postulates a wide-spread viral infection, nontumorigenic when replication competent, but potentially leukemiogenic or carcinogenic

when replication-incompetent viral genomes infect cells with specific chromosomal modifications.(300)

5.6 Hormonal factors

Schmiegelow et al present the adrenal hypothesis: the risk of childhood ALL is reduced when early childhood infections induce qualitative and quantitative changes in the hypothalamus-pituitary-adrenal axis that increase plasma cortisol levels. This may directly eliminate leukemic cells as well as preleukemic cells for the ALL subsets that dominate in the first 5-7 years of life and may furthermore suppress the Th1-dominated proinflammatory response to infections, and thus lower the proliferative stress on pre-existing preleukemic cells.(301)

Active thyroid hormone T3 affects expression of genes that encode for angiogenic proteins like adrenomedullin or vascular endothelial growth factor and erythropoietin, as well as for glucose transporters and phospho fructokinase that determine glucose use. Interestingly, those target genes are also hypoxia inducible and under the control of the oxygen-dependent transcription factor hypoxia-inducible factor (HIF)-1. Some studies have reported that T3 stimulates HIF-1 activation, which intimately links T3 and HIF-1 induced gene expression. Otto et al found that T3 had no direct effect on transcription of HIF-1alpha, but activation of the thyroid hormone receptor beta/retinoid X receptor alpha heterodimer by T3 stimulated expression of the hepatic leukemia factor, which increases HIF-1alpha gene expression.(302)

5.7 Diabetes

Hyperglycemia-induced increase in the production of ROS is proposed to be an initial step in the pathogenesis of diabetes-induced spontaneous abortions and structural inborn anomalies. One of the key molecules involved is tumor necrosis factor-alpha (TNF-alpha): its expression is regulated by ROS and it regulates ROS production in turn. This cytokine may play a dual role in the pathogenesis of diabetes-induced embryopathies. It may act both as a mediator of diabetes-induced embryotoxic stimuli leading to the death of peri-implantation stage embryos and, possibly, as a suppressor of diabetes-induced apoptosis in post-implantation stage embryos. It also appears that TNF-alpha fulfills these functions via interaction with leukemia inhibitory factor (LIF) and the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB).(303)

5.8 Vitamin D

Vitamin D metabolites have been shown to promote differentiation of leukemia and lymphoma cells.(304) Abe et al (305) and Mangelsdorf et al (306) have shown that mouse and human cancer cells can return to normal morphology following administration of these metabolites.

5.9 Selenium

Selenium (Se) is a trace element contributing to the structure of antioxidant system that saves cells from ROS. Low serum Se levels have been reported in pediatric and adult patients with cancers. On the other hand, hair Se levels, predicting the long-term body Se status, have been reported in only adult patients with cancer. A Turkish study found that hair Se levels

of the children with leukemia and lymphoma, especially those of malnourished patients, were lower than those of controls. Additional studies are needed to determinate whether low levels of hair Se may play a role in carcinogenesis.(307)

5.10 Discussion

The literature reveals that environmental hazards cause adverse health effects that include sterility, infertility, embryotoxicity, LBW, skin lesions, neurodevelopmental defects, immunologic disorders, and cancer.(308) As an entity, neonatal tumors provide a unique window of opportunity to study tumors in which minimal environmental interference has occurred.(309) The pediatrician must take action not only against exogenous agents that induce cancer, but also against exposures that begin in utero and lie latent or accumulate throughout life to give rise to cancers in the years ahead.(310) To date few clear preventative measures for childhood leukemia have emerged, except the complete avoidance of first trimester X-rays in pregnancy; a healthy diet with adequate oral folic acid intake both preconception and early in pregnancy; and the early exposure of children to other children outside the home.(27)

Limited data from single or multiple institutions suggest that radiation doses vary within and between medical institutions and among countries. Thus, nationwide surveys are needed in many countries, particularly for higher-dose procedures such at CT, nuclear medicine studies and fluoroscopically-guided diagnostic procedures. It is also critical to collect population-based dose data to estimate doses to embryos and fetuses from maternal obstetric and non-obstetric medical radiologic procedures.(98)

The relative simplicity of the tumor genetics of the common subtypes of leukemia and the availability of archived material in the form of archived neonatal blood spots (ANB or Guthrie cards) has permitted the tracing of many genetic events to fetal origins using sensitive amplification methods.(250) Klotz el demonstrated the feasibility of linking newborn blood spots, population-based cancer incidence data and birth certificate data. They showed the design avoids issues of participation bias by cases and controls and can be used to investigate interactions of susceptibility genes and xenobiotics in semi-ecological studies. It can also be useful for generating or testing hypotheses on associations of other pediatric illness and environmental contaminants.(311) In the US, state policies are rapidly evolving and there is ongoing discussion regarding dried blood spot (DBS) storage and secondary research uses. Currently, population-based DBS studies can be conducted in a limited number of states; fortunately, many have large populations to provide reasonably sized pediatric subject groups.(312)

The newer methods of genome analyses complemented by studies involving the proteome as well as host polymorphisms will have a profound impact on the diagnosis and management of childhood ALL.(313) A rapidly expanding array of technologies include sequencing of the whole genome, exome, transcriptome, tyrosine kinome, and microRNAs, expression arrays, proteomics, methylation, phosphorylation, copy number, gene polymorphisms, and leukemia cell growth in xenograft models.(314)

Different methods of spatial clustering in case-control data have been proposed in recent years.(315) Future research should minimize case and control selection bias, distinguish between different SES measures and leukemia subtypes and consider timing of exposures

and cancer outcomes.(35) Accurate exposure assessment remains a challenge; future epidemiological studies need to assess gene-environment interactions and use improved exposure measures, including separate parental interviews, specific exposure questions, and semi-quantitative exposure measures that can be used to confirm information obtained through questionnaires.(129)

Multidisciplinary collaboration in therapeutic research in childhood cancer has been responsible for enormous improvements in outcomes.(316) In 1994, the US National Cancer Institute funded the Childhood Cancer Survivor Study, a multi-institutional research initiative designed to establish a large and extensively characterized cohort of more than 14,000 5-year survivors of childhood and adolescent cancer diagnosed between 1970 and 1986. This ongoing study, which reflects the single most comprehensive body of information ever assembled on childhood and adolescent cancer survivors, provides a dynamic framework and resource to investigate current and future questions about childhood cancer survivors.(317)

While neonatal disorders, diarrhea, pneumonia, and malaria as well as being underweight account for most of the child deaths worldwide, children's health discussions in Europe and the US focus on other issues such as asthma, neurodevelopmental disorders, male genital malformations, and childhood cancer.(318) Global studies of childhood cancer provide clues to cancer etiology, facilitate prevention and early diagnosis, identify biologic differences, improve survival rates in low-income countries by facilitating quality improvement initiatives, and improve outcomes in high-income countries through studies of tumor biology and collaborative clinical trials.(319) These challenges provide an opportunity

for collaborative interaction between hematologists and policy makers worldwide.(320) The dramatic historical decrease in mortality from childhood cancer is directly related to cooperative group clinical research.(321) Current international collaborations, for example in CLIC (the Childhood Leukemia International Consortium) represent an important step forward.(42) Twinning partnerships between a well-established individual institution or study group and a pediatric cancer unit in a developing country has proved to be the most successful strategy to date.(130, 131)

As countries work together, we have a renewed hope that the causes of childhood leukemia will be unlocked in the foreseeable future. As highlighted throughout this dissertation, a common cause for all types and subtypes of this malignancy is highly unlikely. Deeper insights into the pathogenesis of childhood leukemia will rely on large-scale and combined epidemiological and biomolecular studies.(50)

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