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The Relationships of Infant and Childhood Diet to Growth and Acute Lymphoblastic Leukemia

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The Relationships of Infant and Childhood Diet to Growth and Acute Lymphoblastic Leukemia

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

December 2016

Dedication

Dedicated to my father, for always encouraging and supporting my education.

Acknowledgements

My thanks to Department of Nutritional Sciences and all the past and present members of the Forman Lab for their help and support.

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The University of Texas at Austin, 2016

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Diet during infancy and childhood can affect growth, onset of puberty and disease susceptibility throughout the life course. The goal of this research was to describe the associations of early life diet (birth – five years of age) with hormone levels and pubertal development in healthy adolescent females and with the risk of pediatric acute lymphoblastic leukemia (ALL), the most common form of pediatric cancer, in a population of boys and girls. Chapter 1 summarizes what is known about the early life diet and childhood growth, hormone levels and risk of acute lymphoblastic leukemia. It identifies gaps in the literature which led to the research described in this dissertation. Chapter 2 discusses findings on the effects of early life diet on serum insulin like growth factor-1 levels and breast development in healthy adolescent females. Child's weekly dairy consumption from 3-5 years was inversely associated with the odds ratio of thelarche whereas child's weight and maternal overweight during pregnancy were positively associated with the odds ratio of thelarche at 10.8 years. Chapter 3 discusses identification of two novel risk factors for pediatric ALL: longer duration of milk formula feeding and later introduction of solids foods. Chapter 4 describes research into windows of susceptibility for solid food introduction in ALL. Compared to children introduced to solids before 6 months of age, children introduced to solid foods at or after 7 months of

age are at increased odds of ALL with a dose-response relationship between age at introduction to solids and the odds ratio of ALL. Potential mechanisms for the associations reported in chapters 3 & 4 are discussed. Chapter 5 details the association of age- and sex-adjusted height and weight at time of diagnosis with the odds ratio of ALL. The relationship of height at diagnosis to ALL is unclear, owing in part to inconsistencies in study methodology. Using a population of matched controls, we report no association of height at diagnosis with ALL. Children with low weight-for-age or weight-for-height were at increased odds of ALL. Finally, chapter 6 summarizes these findings and discusses their public health implications.

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Chapter 1: Introduction

INFANT DIET AND CHILDHOOD GROWTH: LINKS FROM EARLY LIFE TO DISEASE RISK

It is now understood that growth *in utero* as well as in infancy and early childhood are determinants of lifetime weight status, hormone levels and health outcomes. Infants who are born premature, low birthweight (< 2,500 grams) of small-for-gestational-age (weight below the 10th percentile adjusted for gestational age) are at risk of acute complications, developmental delays and cardiovascular disease in adulthood[1]. Indeed, the association of low birthweight with cardiovascular disease is even evident in the offspring of women who were themselves low birthweight[1]. Macrosomia or high birthweight (> 4,000 grams) also carries an increased risk of cardiovascular disease in later life[1] as well as of pediatric acute lymphoblastic leukemia (ALL) and other forms of pediatric cancers[2-5]. These risks may be compounded by 'catch-up growth', a period of rapid growth in early life following abnormal fetal growth[1,6]. It is clear therefore that growth both *in utero* and in early life is influential in establishing one's lifelong disease risk.

Infant nutrition exerts a powerful influence on early life growth and development. A large body of research has demonstrated that exclusively breastfed infants gain weight less rapidly during the first year of life than do exclusively formula-fed infants[6-21]. This difference may be explained by the lower mean calorie and protein content of breastmilk relative to commercial milk formula[12,19,22-24], the presence of bioactive compounds like leptin, adiponectin and human milk oligosaccharides (HMOs) in breastmilk[25-28] and the greater role of the infant in determining satiety during breastfeeding as compared to bottle feeding[17,29,30]. Breastfeeding also attenuates the association of high birthweight with rapid growth in infancy and confers protection against later life obesity[14,15,24,31-34].

As a child transitions from breastmilk or infant formula to a diet of solid foods, dietary protein content remains important in growth and development. Higher intakes of milk and animal protein during childhood have been associated with more rapid growth during childhood[12,35-37]. The biological mechanisms by which milk formula and animal protein intakes increase growth in early life are discussed in the following section. These mechanisms are also implicated in the etiologies of pediatric ALL and earlier onset of puberty, the two principal outcomes of this research.

PUTATIVE MECHANISMS FOR INFANT FEEDING-CHILDHOOD GROWTH ASSOCIATIONS

Dietary protein intake and IGF-1 in infants and children

Commercial, cow's milk-based infant formulas and cow's milk have higher protein and calorie content on average than breastmilk[23,38]. In infants, dietary protein intake is a determinant of serum insulin-like growth factor 1 (IGF-1)[20,23,36,39]. Several studies of infant feeding practices have compared IGF-1 levels among breast- and formula-fed infants. In general, serum IGF-1 levels are higher among infants fed milk formula or cow's milk than among infants fed breastmilk[19,20,23,36].

A randomized clinical trial which assigned infants to a low-protein formula, high-protein formula or breastfeeding reported a median free IGF-1 level among infants in the high protein arm which was twice as high as infants in the breastmilk arm (0.60 ng/mL vs. 0.31 ng/mL)[23]. IGF-1 levels were positively associated with weight gain up to 6 months of age in this study. A prospective cohort study of infant feeding, IGF-1 levels and growth demonstrated lower weight and body mass index (BMI) Z scores among breastfed as compared to not breastfed infants at 9 and 18 months of age. The authors identified negative dose-response relationships between number of breastfeeding episodes per day and total daily protein intake, serum total IGF-1 and the molar ratio of

serum IGF-1 to insulin-like growth factor binding protein 3 (IGFBP-3), which is considered a marker of bioavailable IGF-1 levels. The median serum total IGF-1 level was 50% lower among infants breastfed six or more times per day than among infants who were not breastfed (25.6 ng/mL vs. 51.6 ng/mL, $p < 0.001$). The median IGF-1/IGFBP-3 molar ratio was 30% lower among infants breastfed six or more times per day than those who were not breastfed ($p < 0.005$)[19]. Animal protein intake in children has also been associated with higher IGF-1 levels in children between 1-6 years of age, as well as with subsequent weight and length gain and body fatness[12,36].

One study examined IGF-1 levels in expressed breastmilk in connection with growth of infants[27]. The authors reported that breastmilk from mothers of infants with high weight gain (> 1,000 g/mo) contained higher IGF-1 levels at 1, 2 and 3 months of age than breastmilk from mothers of infants of the same age with low (< 500 g/mo) or normal weight gain (500 - 1,000 g/mo). At 3 months, breastmilk of mothers whose infants experienced high weight gain had a mean IGF-1 level of 12.20 ng/mL compared to 3.15 ng/mL in breastmilk of mothers whose infants experienced low weight gain ($p < 0.05$).

IGF-1 is a member of a class of hormones known as somatomedins, which are anabolic and promote cell growth and division[40]. In infants and children this is manifested as weight gain and linear growth[41,42]. Higher serum IGF-1 levels in infancy predict more rapid growth, especially gains in length and height[20,36]. These findings led to the development of the hypothesis that milk formula, cow's milk and early life animal protein intake accelerate growth trajectory by increasing serum total and bioavailable IGF-1 levels.

Rapid growth in infancy predicts higher adiposity in childhood and adulthood

Longitudinal studies of growth during infancy and childhood suggest that greater gains in length and fat-free mass during the first year of life predict higher adiposity later in childhood and in adulthood[6,43]. Exclusive breastfeeding duration ≥ 6 months is associated with shorter length during the first year of life and demonstrates protective effects against obesity which are evident as early as 2 years of age and continuing into adulthood[7,9,31,44]. In addition, one study followed children who were randomized to receive supplemental cow's milk or not until a mean age of 25 years. At follow-up, adults who had received supplemental milk as children had lower mean serum IGF-1 concentrations (-8.5 ng/mL compared to the control group, $p = 0.01$). The authors concluded that early life IGF-1 levels program adult IGF-1 levels in an inverse fashion[45].

These data suggest that weight and length gain in the first year of life program adiposity and hormone levels throughout the life course. This relationship has important public health implications. For example, it is known that overweight or obese girls experience menarche earlier than their leaner peers[46]. This association is likely explained in part by programming of hormone levels and body weight by infant and childhood diet. It has been demonstrated that longer breastfeeding during infancy may delay the onset of menarche[47,48] and that serum IGF-1 levels are higher among girls who experience earlier or precocious puberty[49,50]. A meta-analysis of 117 studies on breast cancer risk concluded that every year younger at age of menarche increased the relative risk of breast cancer by 5%[51]. As of September 1, 2016 the Surveillance Epidemiology and End Results group at the National Cancer Institute estimates 246,000 incident cases of breast cancer will be diagnosed in the United States for the year 2016[52]. Thus, declines in mean age at menarche will have non-trivial consequences for chronic disease burden in the United States. In Chapter 2 I describe research on the relationships of infant and

childhood diet to the onset of thelarche (breast development) in a longitudinal study of healthy Norwegian girls.

WHAT IS KNOWN ABOUT INFANT DIET AND PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

Insulin like growth factor-1 exposure and risk of pediatric ALL

Chapters 3, 4 and 5 discuss the associations of infant diet and childhood anthropometrics with pediatric ALL. ALL arises from rapid and aberrant replication of B or T cell populations[53]. There are few known risk factors for ALL; specifically, trisomy 21 and ionizing radiation have been causally linked to ALL[53,54]. High birthweight and large-for-gestational-age have been reported to increase the risk of ALL[2,5,55]. Birthweight is positively associated with IGF-1 levels in umbilical cord blood[56-59]. This hypothesis has been put forward to explain the higher risk of ALL among those born high birthweight or large-for-gestational-age[60].

IGF-1 regulates lymphopoiesis, the differentiation of multipotent hematopoietic stem cells into mature lymphoid cells[61-63]. *In vitro* research has demonstrated that IGF-1 increases the numbers of CD34+CD38+CD10+ lymphoid progenitor cells[61]. These cells are precursors for the pre-B, B and T cells which are affected by ALL[53]. Higher cumulative exposure to IGF-1 may lead to an increase in the number of cells at risk of malignant transformation in ALL[60].

Several lines of evidence suggest the involvement of IGF-1 and other somatomedins in leukemogenesis. Baier et. al. reported high numbers of high affinity IGF-1 receptors expressed in T cell and pre-B cell ALL cell lines[64]. Another group identified autocrine expression of IGF-1 in leukemias driven by the t(9;22)(q34.1;q11.2) fusion gene ("Philadelphia chromosome") and found that inhibition of IGF-1 decreased

proliferation and increased apoptosis[65]. Badr et. al. reported higher serum IGF-1 levels among incident ALL cases than among age- and gender-matched controls (mean of 454.9 ng/mL in cases compared to 99.3 ng/mL in controls; $p < 0.001$)[66]. Other authors have reported alterations in IGF-1 and IGFBP-3 levels in serum or bone marrow of leukemia patients, which have been summarized in a review article[67]. The observations that formula feeding is associated with higher serum IGF-1 levels and that higher serum IGF-1 levels may increase the risk of pediatric ALL led to the development of specific aims 2-4 of this dissertation.

DISSERTATIONS AIMS ADDRESS GAPS IN THE LITERATURE

The literature provides considerable evidence for possible relationships of formula feeding with ALL and pubertal development as well as of formula feeding and age at introduction to solids with ALL. Despite this, nutritional epidemiology has not investigated these topics extensively. In particular, only one previous study has investigated the association of milk supplementation with risk of ALL[68]; no studies have investigated the effect of timing of introduction to solid foods on ALL, and little has been done to characterize the relationship of infant and childhood diet with anthropometrics and hormone levels in adolescents and adults[45]. The above referenced research and gaps in our current understanding of infant feeding and disease outcomes led to the development of 4 specific aims for this dissertation.

SPECIFIC AIMS

Specific aim 1 is to determine whether infant feeding practices and milk and animal protein intake from 3-5 years are associated with serum IGF-1 at 10.8 years and with the odds ratio of thelarche at 10.8 years and Tanner breast stage 3 or above at 12.9 years in girls.

Specific aim 2 is to determine whether longer cow's milk formula feeding is associated with the odds ratio of pediatric acute lymphoblastic leukemia.

Specific aim 3 is to determine whether later age at introduction to solid foods is positively associated with pediatric ALL.

Specific aim 4 is to determine whether height-for-age, weight-for-age and weight-for-height at time of diagnosis/interview are associated with pediatric ALL.

Chapter 2: Effects of Infant and Childhood Diet on Pubertal Development in Healthy Girls

This section was published as "Schraw JM, Ogland B, Dong YQ, Nilsen ST, Forman MR. In utero preeclampsia exposure, milk intake and pubertal development. *Reproductive toxicology (Elmsford, N.Y.)*. Dec 12 2014."[69] Jeremy Schraw drafted the manuscript and conducted statistical analyses. Bjorn Ogland collected data, translated study documents into English and revised the manuscript. Yongquan Dong maintained and provided data and reviewed the statistical analyses. Stein Tore Nilsen and Michele Robin Forman designed the study, collected data and revised the manuscript.

ABSTRACT

Cord blood insulin-like growth factor-1 (IGF-1) concentrations are lower in preeclamptic (PE) than normotensive (NT) pregnancies. PE offspring have increased risk of cardiovascular disease and decreased risk of some cancers including breast. We examined the effects of PE exposure *in utero*, infant feeding and childhood diet at 3-5 years on IGF-1 and breast development in 194 female offspring who were followed from birth until follow-ups at 10.8 and 12.9 years. Diet was not associated with serum IGF-1 levels at 10.8 years. PE exposure was associated with reduced odds of thelarche at 10.8 years only among exclusively breastfed girls. Milk, butter and ice cream consumption at 3-5 years was inversely related to the OR of breast development at 10.8 years. Child's weight and maternal overweight were positively associated with breast development at

10.8 years; child's height and weight were positively associated with breast development at 12.9 years.

Keywords: preeclampsia, infant feeding, childhood diet, dairy consumption, breast development, puberty, developmental programming

INTRODUCTION

Preeclampsia (PE) is a pregnancy disorder characterized by inadequate development of the spiral arteries that supply blood to the placenta and maternal hypertension and proteinuria[70]. Maternal serum androgen levels, notably testosterone and androstenedione, are elevated in PE pregnancies while cord blood insulin-like growth factor 1 (IGF-1) concentrations are reduced[57,71-79]. Beyond the immediate risks PE pregnancies pose to the mother and neonate, their androgenic nature has been hypothesized to affect chronic disease risk in both[80,81]. Indeed, offspring of PE pregnancies are at increased risk of cardiovascular disease but decreased risk of breast and prostate cancers[82-86]. PE mothers are at decreased risk of breast cancer and the reduction in risk is larger if the offspring of the index pregnancy is male (relative risk 0.79, 95% CI 0.60 – 0.90)[80,83,84]. If the unique hormonal milieu of PE pregnancies causes developmental programming in offspring and reprogramming in mothers resulting in

long-term changes to the hormonal profile, it is possible that these changes may contribute to the observed incidence rates of chronic diseases among PE mothers and offspring.

Diet in infancy and childhood impacts serum hormone levels and adult chronic disease risk. In particular cow's milk and cow's milk formula consumption are directly associated with higher serum IGF-1 concentrations and risk of obesity and may cause reprogramming of adult IGF-1 concentrations[14,87]. Research on the relationships between infant feeding, childhood diet and age at onset of puberty, an intermediate marker for adult chronic disease, has been inconsistent. Neither the effects of diet on pubertal timing or the ages at which children are susceptible to dietary programming effects on pubertal timing are well understood[88]. Further, these studies have focused on age at menarche and peak height velocity, used incomparable methodologies and have not explored associations of infant feeding practices with more proximal events like onset of thelarche (breast development). The objectives of this study were to compare serum IGF-1 levels and breast development at 10.8 years in girls according to PE exposure *in utero*, infant feeding practices (breast and milk formula feeding, age at introduction to solid foods) and childhood milk, butter and ice cream and animal protein intake. We hypothesized that PE children would have lower IGF-1 levels than NT children at 10.8 years and that infancy and childhood milk and animal protein intake would be negatively associated with serum IGF-1 at 10.8 years. We use a life-course approach to address *in utero*, infant and childhood exposures on IGF-1 concentrations and breast development in early puberty in an effort to identify early exposures related to chronic disease.

MATERIALS AND METHODS

Data collection

Umbilical cord blood samples and demographic data were collected from participants in a prospective study of births at Rogaland Central Hospital in Stavanger, Norway between January 1993 and December 1995. Preeclamptic (PE) women were identified from among mothers who delivered at the hospital during this time as described previously[57]. Briefly, inclusion criteria for PE mothers were a diagnosis of PE during the index pregnancy, a live birth event at Rogaland Central Hospital during 1993 – 1995, Norwegian residency, mentally competent and not treated with chemotherapy or radiotherapy during the prior year. PE was diagnosed based on blood pressure and proteinuria levels from mid-pregnancy on and further classified as mild, moderate or severe according to the CLASP criteria as specified previously[70,89]. Two normotensive (NT) women who delivered at the hospital during the study period were matched to each case of PE; one who delivered a child of the same sex on the same day and a second on the basis of maternal age.

Participants were invited to follow-up studies at 10.8 and 12.9 years. 288 mother-daughter dyads participated in the first follow-up, of which 180 of the index pregnancies were NT and 108 were PE. Of these, 194 pairs (119 NT, 75 PE) returned and provided data at 12.9 years. Anthropometrics were measured and Tanner breast stage was assessed using palpation by trained pediatric research nurses according to protocols described

previously[90]. Tanner stage was recorded as 1-5 and nurses were blind to the PE status of the participating children.

Mothers completed a questionnaire to assess child and maternal health through the life course and daughter's diet during infancy and childhood. Regarding maternal exposures, data were collected on maternal employment and physical activity, smoking, alcohol, coffee and tea drinking, anthropometrics, family history of disease and mother's health conditions. Maternal weight was categorized as normal weight (BMI 18.5 – 24.99), overweight (BMI 25 – 29.99) or obese (BMI 30 or above). Mothers were asked whether they breastfed the index child and for how long, whether they fed infant formula, its type and the ages at which the child received formula and when the child began receiving solids and cow's milk. Mothers completed a semi-quantitative food frequency questionnaire of child's diet from 3-5 years of age originally derived from the Mother's Cohort of the Nurse's Health Study II[91]. Pre-pregnancy weight, pregnancy weight gain, mode of delivery, infant birthweight and birth length, child's medication use, history of infection and history of hospitalization were abstracted from medical records using the unique identifying number provided at birth by the Norwegian government.

Diet was examined in chronological order using data from infancy and then childhood. Breastfeeding and formula feeding duration and age at introduction of solids were reported in 3 month increments except for the first week of life i.e. < 1 week, 1 week - 3 months, 3 - 6 months, 6 - 9 months or > 9 months. Children who were breastfed for < 1 week were considered exclusively formula fed. Few parents reported introducing solids before 3 months or after 9 months (n = 2 for each) so only the effects of

introducing solids at 3 -6 months and 6 – 9 months were considered. How frequently the child consumed animal and dairy proteins was assessed using a food frequency questionnaire. Parents reported child's dietary intake from the ages of 3-5 years according to the following categories: never, 1-3 times per month, 1 time per week, 2-4 times per week or 5 or more times per week. The questionnaire asked mothers to report how often the child consumed the following animal foods from 3-5 years: eggs, hot dogs and sausage, lunch and deli meats, minced meats, pork, beef, lamb, chicken, turkey, fish and seafood and liver. Child's frequency of animal protein consumption per week was computed by assigning a numerical score equal to the median of the frequency category to each response and taking the sum of these scores across all categories of animal foods. "Never" was assigned a value of 0 and "5 or more times per week" was assigned a value of 5. The same procedure was followed to compute the number of times per week that the index child consumed milk, ice cream and butter. Data were not collected on cheese or yogurt consumption so these data could not be included in the estimate of total dairy consumption. In sensitivity analyses, the weekly frequency of milk intake reported according to the same categories as the abovementioned foods replaced the weekly frequency of dairy consumption.

Biospecimen analysis

Overnight fasting blood samples were collected in heparinized tubes from children at follow-up. Blood samples were immediately frozen at -80^{o} C and stored at Stavanger University Hospital. Blood samples were shipped to Esoterix Laboratory,

LLC (Calabasas Hills, California) for analysis of insulin like growth factor-1 (IGF-1) by radioimmunoassay and high performance liquid chromatography-mass spectrometry. Limits of detection were 15 ng/mL for IGF-1. The Intra-assay coefficient of variation was 10.6%.

Statistics

Tests for differences in the means of continuous variables between PE and NT girls were computed using the Student's t tests. χ^2 or likelihood ratio tests were used to test for differences in proportions of girls classified by Tanner breast stages, by infant feeding patterns and by PE status. Descriptive data were presented as proportions and means ± standard errors except for cord blood levels of IGF binding proteins which were non-normally distributed and for which medians ± interquartile ranges were reported. Serum IGF-1 levels were natural-log transformed in subsequent analysis to reduce skewness and normalize their distributions.

Linear regression models were computed to model the natural log of serum IGF-1 levels (the dependent variable) with the following independent variables: PE status, duration of breastfeeding, age at introduction of formula, age at introduction of solids, frequency of childhood milk and animal protein consumption, Tanner breast stage, and maternal body mass index. PE status, Tanner stage, duration of breastfeeding, age at introduction to formula and age at introduction to solids were treated as fixed effects. Height, weight, maternal body mass index, average total weekly frequency of milk, butter

and ice cream consumption and average total weekly frequency of animal protein consumption were treated as continuous variables.

Multiple logistic regression analysis was used to model the odds ratio (OR) and 95% confidence interval of thelarche (dependent variable, breast development defined as Tanner breast stage 2+ versus Tanner breast stage 1) in girls at 10.8 years and the OR of being classified as Tanner 3 or above at 12.9 years using the same predictors. Child's age was not included in the models because by design there was minimal variation in the ages of children at follow-up (table 2). PE status was not associated with the natural log of serum IGF-1 at follow-up or with height and weight and there was no evidence of interaction between PE status and any dietary variables (data not shown). Therefore main effects models were run including all PE and NT children simultaneously.

All statistical procedures were computed in IBM SPSS version 21 (© 2012, IBM, Armonk, New York). P-values < 0.05 were considered significant. Adjustments for multiple comparisons were made during post-hoc testing to maintain an α level of 0.05 for the entire set of tests. The method of correction was determined by the statistical procedure and the distribution of the data. When data were natural log-transformed for analysis, results were back-transformed for presentation.

IRB approval

This study was approved by the Regional Committee for Ethics in Medical Research, the Norwegian Data Inspectorate and The University of Texas at Austin (IRB number 2014-04-0036).

RESULTS

Table 2.1 lists birth characteristics, levels of cord blood analytes and infant feeding practices among study participants. PE mothers were younger on average than normotensive mothers ($p < 0.001$). PE girls had lower birthweight, birth length and cord blood IGF-1 concentrations as well as shorter gestational length than their sex-matched NT controls. Neither the proportion of mothers who reported ever breastfeeding, exclusive breastfeeding, ever formula feeding nor the duration of infant feeding practices varied by PE status. Similarly there were no differences in the ages at which children started and stopped receiving infant formula, began receiving solid foods and began receiving cow's milk by sex and PE status (data not shown). There were no differences observed in baseline maternal or birth characteristics between those who consented to participate at first follow-up and those who did not[92].

Table 2.1 Birth characteristics of the study sample

	Means ± standard errors		
Birth Characteristics	Normotensive girls (n=180)	Preeclamptic girls (n=108)	p-value, girls (NT vs. PE)
Maternal age (yr)	**28.7 ± 5.3**	**27.5 ± 4.8**	**0.01**
Gestation length (d)	**280.6 ± 10.9**	**264.5 ± 22.6**	**<0.001**
Birthweight (g)	**3517.3 ± 36.9**	**3026.8 ± 81.6**	**<0.001**
Birth length (cm)	**49.5 ± 0.1**	**47.1 ± 0.6**	**<0.001**
Cord blood			
Cord IGF-1 (ng/mL)	**66.4 ± 2.0**	**57.2 ± 3.2**	**0.01**
Cord IGFBP-1 (ng/mL)	95.2 ±39. 6[1]	96.0 ± 141.7[1]	0.37[2]
Cord IGFBP-3 (ng/mL)	1357.4 ± 506.0	1296.9 ± 560.6	0.29[2]
Infant feeding		Proportions	
% Ever breastfed	93.9	90.7	0.16
% Exclusively breastfed	53.9	52.8	0.48
% Ever fed formula	43.9	44.4	0.93

1. Data are non-normally distributed. Medians and interquartile ranges are reported.
2. P-value derived from Kruskall-Wallis Test rather than t test; post-hoc p-values computed by Mann-Whitney U Test with Bonferroni adjustment.

Table 2.2 lists follow-up characteristics of the study sample. There were no differences in anthropometric measurements at follow-up, infant feeding practices or childhood dietary variables between those lost to follow-up at 12.9 years and those who completed both visits except that there was a marginally significant difference in the likelihood of exclusive breastfeeding (46.8% exclusively breastfed and 48.9% fed both breast milk and formula among those lost to follow up vs. 56.7% and 35.1% among those who participated, $p = 0.06$).

Table 2.2 Follow-up characteristics of children at 10.8 and 12.9 years

	10.8 years (Mean ± S.E.)			12.9 years (Mean ± S.E.)		
	Normotensive girls (n=180)	Preeclamptic girls (n=108)	p-value	Normotensive girls (n=119)	Preeclamptic girls (n=75)	p-value
Age (yrs)	10.8 ± 0.15	10.8 ± 0.07	0.646	12.9 ± 0.01	12.9 ± 0.01	0.799
Height (cm)	147.5 ± 0.8	146.8 ± 0.7	0.86	159.6 ± 0.6	158.8 ± 0.8	.399
Weight (kg)	38.2 ± 0.6	39.8 ± 0.9	0.41	47.5 ± 0.8	49.4 ± 1.2	.153
Serum IGF-1 (ng/ml)[1]	246 ± 143	264 ± 153	0.799	N/A	N/A	
			Tanner breast stages			
% Stage 1	40.8	43.8		3.4	6.7	
% Stage 2	35.1	37.1	0.801	22.7	17.3	0.621
% Stage 3	23.0	18.1		47.1	49.3	
% Stage 4	1.1	1.0		26.9	26.7	

1. Serum IGF-1 measurements were not measured at 12.9 years. Data at 10.8 years are non-normally distributed. Medians ± interquartile ranges are reported.

A higher proportion of mothers who exclusively breastfed than those who both breast and formula fed were breastfeeding for > 9 months (77.7% vs. 15.9% respectively, p <0.001). From the ages of 3-5 years egg consumption was more frequent among NT than PE girls with 18.7% of PE mothers reporting their child never consumed eggs vs. 4.6% of NT mothers (p = 0.003). No differences in child's consumption of pork, beef and lamb, chicken and turkey, fish and seafood or liver were observed by PE status. The

mean reported frequency of animal protein consumption was 9.3 ± 3.8, with a range from 0 to 28.5 times per week. The frequency of consumption did not vary by PE status. Milk was the dairy food consumed most often (14.8 times per week on average) followed by butter (9.3 times per week on average).

Results of logistic regression models are presented in Table 4. There was no significant difference in Tanner breast stage or serum IGF-1 levels by PE status. No significant associations were observed between dietary variables and the natural log of serum IGF-1 in univariate analysis. PE status and dietary variables were not associated with serum IGF-1 levels in the adjusted model; however height and Tanner stage were significantly positively associated with serum IGF-1 (data not shown). Each 1 cm increase in height was associated with a 1.7% increase in serum IGF-1. Each increase in Tanner stage from 1 to 4 was associated with an increase in serum IGF-1 concentrations; mean serum IGF-1 was significantly different for every pairwise comparison except for Tanner stage 3 compared to stage 4. Specifically, compared to Tanner 1 girls, mean serum IGF-1 was 20.9% higher for Tanner 2 girls, 48.1% higher among Tanner 3 girls and 132.8% higher among Tanner 4 girls. Neither the duration of breastfeeding nor other dietary variables among the exclusively breastfed and mixed fed children were associated with serum IGF-1 concentrations. To investigate whether cow's milk alone rather than combined milk, butter and ice cream may have an effect on serum IGF-1 we replaced the estimated frequency of these three dairy food groups with the maternal-reported frequency of milk consumption in the models, but results were unchanged (data not shown).

There were significant positive associations between child's weight and maternal BMI of 25 – 29.99 and the OR of thelarche at 10.8 years (table 2.3) whereas the frequency of milk, butter and ice cream consumption was negatively associated with the OR of thelarche at that age. At 12.9 years, neither PE exposure, maternal BMI nor any dietary variables were significantly associated with the OR of Tanner breast stage 3 or above (compared to Tanner breast stage 1 or 2) (data not shown). Child's current weight and height were both significantly positively associated with the OR of more advanced breast development. Each 1 kg increase in weight was associated with an OR of 1.16 (1.06 – 1.27) and each 1 cm increase in height was associated with an OR of 1.14 (1.04 – 1.25). Maternal BMI was not related to breast development.

Table 2.3 Unadjusted and adjusted odds ratios for thelarche at 10.8 years by infant feeding practices, age at introduction to solids and childhood diet

	Unadjusted[3]	**Early life model[4]**	**Childhood model[5]**	**Adjusted model[6]**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Duration of breastfeeding				
1 week – 3 months	1.00	1.00	-	1.00
3 – 6 months	1.29 (0.49 – 3.37)	1.46 (0.45 – 4.74)	-	2.34 (0.55 – 9.96)
6 – 9 months	0.99 (0.44 – 2.25)	1.27 (0.37 – 4.42)	-	2.81 (0.64 – 12.36)
> 9 months	1.41 (0.68 – 2.91)	1.80 (0.51 – 6.38)	-	4.48 (0.99 – 20.16)
Age started formula				
No milk formula	1.00	1.00	-	1.00
< 3 months	0.81 (0.41 – 1.61)	0.64 (0.19 – 2.17)	-	1.29 (0.30 – 5.49)
3 - 6 months	1.06 (0.54 – 2.11)	1.16 (0.39 – 3.45)	-	2.63 (0.73 – 9.50)
6 - 9 months	0.67 (0.30 – 1.50)	0.58 (0.22 – 1.52)	-	0.69 (0.21 – 2.31)
> 9 months	0.67 (0.16 – 2.78)	0.42 (0.09 – 1.98)	-	0.74 (0.12 – 4.36)
Age started solids				
3 - 6 months	1.00	1.00	-	1.00
6 - 9 months	0.75 (0.45 – 1.25)	0.62 (0.35 – 1.10)	-	0.60 (0.30 – 1.22)
PE exposure	0.86 (0.53 – 1.41)	0.73 (0.42 – 1.27)	-	0.57 (0.28 – 1.14)
Per extra weekly dairy consumption event[1]	0.98 (0.96 – 1.00)	-	**0.98 (0.95 – 1.00)**	**0.97 (0.95 – 1.00)**

Table 2.3 Unadjusted and adjusted odds ratios for thelarche at 10.8 years by infant feeding practices, age at introduction to solids and childhood diet (continued from page 22)

Per extra weekly protein consumption event[2]	0.97 (0.91 – 1.04)	-	0.95 (0.88 – 1.03)	0.95 (0.87 – 1.05)
Maternal BMI (kg/m^2)				
18.5 – 24.99	-	-	1.00	1.00
25 – 29.99	-	-	**2.08 (1.04 – 4.16)**	**2.63 (1.19 – 5.81)**
≥ 30	-	-	0.96 (0.39 – 2.40)	1.19 (0.42 – 3.40)
Height (cm)	-	-	0.98 (0.90 – 1.07)	1.03 (0.96 – 1.11)
Weight (kg)	-	-	**1.24 (1.12 – 1.36)**	**1.16 (1.08 – 1.25)**

1. Includes milk, butter and ice cream.
2. Includes eggs, hot dogs and sausage, lunch/deli meats, minced meats, pork, cattle, beef, lamb, chicken, turkey, fish and other seafood and liver.
3. Univariate results.
4. Early life model includes infant feeding variables, age at introduction to solids and PE exposure.
5. Childhood model includes childhood diet variables, maternal BMI, child's height and weight.
6. Adjusted model contains all variables in the early life and childhood models.

When these analyses were restricted to exclusively breastfed children (N=154, table 3.4), child's weight and maternal BMI 25 – 29.99 remained significantly associated with the OR of thelarche at 10.8 years however the effect of childhood milk, butter and ice cream consumption was attenuated and became non-significant. Among exclusively breastfed children PE status was negatively associated with OR of thelarche at 10.8 years. Current height and weight remained the only variables significantly associated with the OR of Tanner breast stage 3+ at 12.9 years (data not shown).

Table 2.4 Unadjusted and adjusted odds ratios for thelarche at 10.8 years among exclusively breastfed girls

	Unadjusted[3]	**Early life model[4]**	**Childhood model[5]**	**Adjusted model[6]**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Duration of exclusive breastfeeding				
6 – 9 months	0.82 (0.36 – 1.89)	0.68 (0.28 – 1.66)	-	0.59 (0.19 – 1.82)
> 9 months	1.00	1.00	-	1.00
Age started solids				
3 - 6 months	1.00	1.00	-	1.00
6 - 9 months	0.75 (0.45 – 1.25)	0.58 (0.27 – 1.22)	-	0.57 (0.22 – 1.44)
PE exposure	0.54 (0.27 – 1.07)	**0.47 (0.23 – 0.97)**	-	**0.29 (0.11 – 0.76)**
Per extra weekly dairy consumption event[1]	0.98 (0.96 – 1.00)	-	0.98 (0.95 – 1.01)	0.97 (0.94 – 1.01)
Per extra weekly protein consumption event[2]	0.97 (0.91 – 1.04)	-	1.05 (0.93 – 1.18)	1.04 (0.91 – 1.18)
Maternal BMI (kg/m^2)				
18.5 – 24.99	-	-	1.00	1.00
25 – 29.99	-	-	**6.29 (2.05 – 19.29)**	**5.71 (1.65 – 19.84)**
≥ 30	-	-	1.17 (0.29 – 4.68)	1.12 (0.25 – 4.93)

Table 2.4 Unadjusted and adjusted odds ratios for thelarche at 10.8 years among exclusively breastfed girls (continued from page 24)

Height (cm)	-	-	1.04 (0.95 – 1.13)	1.01 (0.91 – 1.11)
Weight (kg)	-	-	**1.11 (1.02 – 1.20)**	**1.15 (1.04 – 1.26)**

1. Includes milk, butter and ice cream.
2. Includes eggs, hot dogs and sausage, lunch/deli meats, minced meats, pork, cattle, beef, lamb, chicken, turkey, fish and other seafood and liver.
3. Univariate results.
4. Early life model includes infant feeding variables, age at introduction to solids and PE exposure.
5. Childhood model includes childhood diet variables, maternal BMI, child's height and weight.
6. Adjusted model contains all variables in the early life and childhood models.

DISCUSSION

We investigate using a life course approach two important phenomena in girls, breast development and IGF-1 levels, the latter of which has been considered a marker for premenopausal breast cancer risk[40]. Considering all children, PE exposure *in utero* was not associated with breast development (Tanner Stage B2+ v. B1) at 10.8 years nor with Tanner Stage B3+ at 12.9 years, in accord with one earlier study but not another[93,94]. When the analysis was restricted to exclusively breastfed girls, PE exposure *in utero* was associated with a reduced OR of thelarche in models adjusted for maternal BMI, infant feeding patterns, childhood diet and child's current weight and height.

PE exposure can alter timing of pubertal events; Øgland *et al* have previously demonstrated in this sample that pubarche was more likely to precede thelarche in PE girls compared to NT girls. This finding is consistent with reduced risk of breast cancer among offspring and is hypothesized to be an effect of *in utero* androgen exposure[90,95].

Our results suggest exclusive breastfeeding may also modify the relationship of PE exposure *in utero* with breast development at 10.8 years. Rapid weight gain in early life may mediate the association between premature birth and earlier puberty[96,97] and as compared to formula-fed infants breastfed infants gain weight less rapidly[87]. In another population, breastfeeding reduced DNA methylation differences between children born ≤ 85th percentile of weight-for-gestational-age and children born > 85th percentile at the H19 differentially methylated region. Further, whereas the OR of overweight or obesity among never breastfed children with ≥ 75th percentile methylation at H19 was 22.27 (95% CI 2.07-239.84) there was no effect among breastfed children[98]. Such findings raise the possibility that exclusive breastfeeding may modify developmental programming resulting from *in utero* PE exposure. Only 3 mothers who breastfed exclusively reported breastfeeding for fewer than 6 months, limiting analysis of breastfeeding duration in this group. The association of PE exposure and pubertal development may also be affected by maternal BMI; in a separate analysis of our sample, daughters of PE pregnancies from obese women had higher BMI and larger waist and hip circumferences whereas no such differences were evident when comparing PE and NT daughters of normal weight or overweight mothers[92].

Childhood frequency of milk, butter and ice cream consumption was weakly inversely associated with the OR of Tanner stage 2+ at 10.8 years but not with Tanner 3+ at 12.9 years. A recent systematic review concluded there was a likely association between childhood animal protein intake and earlier puberty assessed by age at menarche and age at peak height velocity[99]. There is less research on dairy consumption and breast

development. In our analysis, child's weight and maternal BMI were more strongly associated with the OR of thelarche and child's height and weight were the only variables significantly associated with breast development at 12.9 years. These findings are consistent with studies showing earlier breast development among girls with greater BMI and accelerated achievement of pubertal milestones among both male and female offspring of overweight or obese mothers[46,100,101]. One potential mechanism for the effect of dairy consumption on thelarche in this population is that it is often associated with lower weight and adiposity in observational studies[102]. In our study, the correlation coefficients between dairy consumption and weight at first and second follow-up were negative but non-significant.

Our research was conducted in Norway where there are restrictions on and therefore limited exposure to environmental contaminants such as bisphenol A and recombinant bovine somatotropin compared to the United States. Thus our findings are most applicable to maternal breast milk and cow's milk absent contaminants in non-European populations. While infant and child diet were not associated with IGF-1 levels, height and Tanner breast stage were associated with serum IGF-1. Both have been previously identified as correlates of serum IGF-1 levels in healthy European children[103].

This study has limitations. First, the childhood diet-outcome associations may have been attenuated by use of a semi-quantitative food frequency questionnaire. The categories of dairy and animal foods on which data were collected were not exhaustive. Some foods - for example cheese and yoghurt - were not reported. The DAFNE study reported the average per capita daily availability (not intake) of cheese products in

Norway to be 38 grams, sixth among ten European countries[104]. Hjartåker et al. reported that the average daily consumption of cheese was 40-43 grams among adult Norwegian women who participated in the European Prospective Investigation into Cancer and Nutrition (EPIC) study[105]. In this sample, cheese accounted for 14% of total dairy consumption. Twelve to thirteen percent of dairy consumption was as 'yoghurt and other fermented milk products' (mean 35-38 g/d). Sixty one percent was from milk with lesser contributions from creams, puddings, ice creams and butter. Norway's per capita cheese consumption was greater than most other European countries whereas its per capita yoghurt consumption was lower. A study of iodine content in the Norwegian diet reported a mean cheese intake of 23 g/d among adult men and 22 g/d among adult women. It is likely that our data underreport frequency of total dairy intake, specifically regarding cheese and to a lesser extent yoghurt, but the extent to which this is true in children is unknown given available data relate to adults. Further research on total dairy consumption among Norwegian children is required to determine both the rates of consumption and whether dairy foods have heterogeneous effects on breast development.

Considering duration of breastfeeding, age at introduction of solids and age at introduction of formula in three-month increments may be inadequate for future studies of the developmental effects of infant feeding practices. Within the three month windows the effects of terminating breastfeeding, introducing formula or solids may in fact be biologically diverse and identify a specific window of susceptibility. This loss of precision may have attenuated our ability to detect associations between infant feeding practices and IGF-1 at 10.8 years due to misclassification of the exposure and potentially

reduced inter-individual variation in the exposure status. However, mothers completed the childhood FFQ at the first follow-up so there is potential recall bias. Likewise, assigning the median value to all responses within the intake category for childhood dietary variables (for example defaulting all responses in the 2-4 times per week category to 3 times per week) fails to accurately reflect heterogeneity in dietary patterns between subjects and may weaken any dietary associations. This is particularly true for subjects who reported frequencies of consumption in the highest, open-ended categories. These individuals are likely to have consumed these foods more often than indicated. Because average serving size was not reported, it is possible children with different frequencies of consumption may in fact have more similar absolute intakes. Conversely, children with the same reported frequency of intake may have different absolute intakes owing to different serving sizes.

A prior study of maternal recall of breastfeeding among Norwegian women after a 20-year interval reported strong correlations between recorded and recalled duration[106], though in other studies maternal recall of childhood diet became less accurate as the elapsed time interval lengthened[107,108]. Hence, it is also possible that assigning the median value to all responses within each intake category may reduce false inter-individual variation introduced by errors in maternal reporting.

CONCLUSIONS

PE exposure was associated with reduced odds of thelarche at 10.8 years among exclusively breastfed girls only. Increasing frequency of childhood milk, ice cream and

butter consumption was negatively related to the OR of thelarche at 10.8 but not to the OR of having more advanced breast development at 12.9 years. In contrast, infant feeding patterns were not associated with breast development at either age. Increasing weight was consistently associated with more advanced breast development, as were maternal BMI at 10.8 years and offspring's height at 12.9 years. Infant feeding and childhood diet were not associated with serum IGF-1 levels at 10.8 years. Concordant with other published data, being taller and more advanced breast stage were both found to correlate with higher serum IGF-1 levels. Future research needs to determine whether PE offspring experience changes in the rate of subsequent pubertal development, whether diet more proximal to puberty could influence development and whether the reported association may be due to particular dairy foods or to another exposure associated with dairy consumption patterns.

ACKNOWLEDGEMENTS

The authors extend their thanks to all participants in the Stavanger cohort study, to Dr. Donald Walt Chandler at Esoterix Laboratories for his contributions to the analysis of hormone levels and to the Bruton Centennial Fellowship for its support of nutritional sciences research at the University of Texas. This study was supported by internal funding from the National Cancer Institute, NIH and the Folker Foundation, Stavanger Norway.

Chapter 3: Infant Feeding Patterns are Associated with Pediatric Acute Lymphoblastic Leukemia

This section was originally published as "Schraw JM, Dong YQ, Okcu MF, Scheurer ME, Forman MR. Do longer formula feeding and later introduction of solids increase risk for pediatric acute lymphoblastic leukemia? *Cancer causes & control : CCC.* Oct 24 2013."[109] Jeremy Schraw designed the research, drafted the manuscript and conducted statistical analyses. Yongquan Dong supervised statistical analyses. Mehmet Fatih Okcu collected data and revised the manuscript. Michael Scheurer collected and maintained data and revised the manuscript. Michele Forman designed the research and revised the manuscript.

ABSTRACT

Milk formula feeding can elevate insulin-like growth factor-1 levels, possibly impacting leukemogenesis. The intent of the current study is to examine the associations between infant feeding practices and age at introduction of solids on risk of childhood acute lymphoblastic leukemia (ALL). Incident cases of infant and childhood (aged ≤ 14 years) ALL (N=142) were enrolled in a case-control study. Cases were frequency matched on age, sex, race and ethnicity to two sets of controls (N =284 total). Multivariable logistic regression was used to determine the association between infant

feeding practices and age at the introduction of solids and the odds ratio of ALL. In adjusted multivariable analyses, each additional month of formula feeding was associated with a 1.17 (1.09-1.25) odds ratio; each additional month of age at introduction of solids was associated with a 1.18 (1.07-1.30) odds ratio. In this study, longer duration of formula feeding and later age at the introduction of solid foods were independently associated with increased risk of ALL. Additional studies are needed to address the factors influencing duration of formula feeding and delayed introduction of solids. The results support the potential role of energy balance in early life as a contributor to risk for pediatric acute lymphoblastic leukemia.

INTRODUCTION

The etiology of acute lymphoblastic leukemia (ALL) is not well understood. A few strong risk factors have been identified, such as a diagnosis of Down syndrome or exposure to ionizing radiation *in utero*[53]. Insulin like growth factor-1 (IGF-1) and growth hormone (GH) are regulators of lymphopoietic stem cell proliferation and lymphoid stem cells express IGF-1 and insulin receptors, with receptors on leukemic cells possessing greater affinity[61,110,111]. Therefore, elevations in bioavailable IGF-1 could subject hematopoietic cells to a proliferative stress and encourage the growth of leukemic cells. High IGF-1 exposure has been associated with risk of ALL directly[66] as well as through high birthweight (≥ 4000 g), large for gestational age and taller standing height than age-matched controls[112,113]. Evidence for the association between accelerated intrauterine growth and ALL is strong. Both our group and others report an increased risk among

high birthweight (HBW) and large for gestational age (LGA) infants[112-114]. One study reported a 41% increased risk (OR 1.41, 95% CI 1.08-1.84) among HBW infants as compared to the normal birthweight group (2500-4000 gr)[114]. Among LGA infants the odds ratio of ALL was 45% higher compared to the appropriate for gestational age (OR 1.45, 95% CI 1.07-1.97). The association between childhood cancer and the IGF system, summarized in an excellent review[67], stimulated the current line of investigation.

Within the last decade, the influence of infant feeding practices on serum IGF-1 has become clearer. Cow's milk and cow's milk formula have been shown to elevate bioavailable serum IGF-1[19,20], and a dose-response has been established between higher protein content in formula and higher free IGF-1[23]. While the literature suggests that prolonged breastfeeding (≥ 6 or 12 months) may have a weak protective effect against ALL[115,116], the relationships between cow's milk formula feeding and the age at the introduction of solid foods and risk of diagnosis have not been well characterized. Timing of the introduction of solids foods was considered as an exposure because it is known to be associated with breastfeeding duration[117,118]. The objective of this paper is to characterize the relationship between infant feeding practices and age at the introduction of solids and pediatric ALL in a case-control study of Texas children.

MATERIALS AND METHODS

Subjects

Cases were children aged ≤ 14 years newly diagnosed with ALL at the Texas Children's Cancer Center (TCCC) between 1997 and 2011. Controls were recruited from

two groups: healthy children attending well-child visits at Texas Children's Hospital (TCH) and satellite clinics, whose mothers completed the TCCC questionnaire; the second group of controls were mother-offspring dyads in Houston, San Antonio and Austin, Texas randomly selected from those who participated in formative research for the National Children's Study (NCS). Exclusion criteria for the control group were a diagnosis of cancer or of any condition known to be associated with pediatric cancer risk. Controls were frequency matched 2:1 to cases on age (± 1 year), sex, race and ethnicity. 179 cases consented and were enrolled in the study. Of these, 37 were excluded because infant feeding data were missing. Therefore 142 cases and 284 controls were included in the final analysis. There were no significant differences between included and excluded cases by race, gender, ethnicity or age at diagnosis. The overall participation rate for cases diagnosed at TCCC was 85% and for controls recruited through TCH-affiliated clinics the participation rate was 90%. This study was approved by the Institutional Review Boards of Baylor College of Medicine and The University of Texas at Austin. Written informed consent was obtained from the parents of cases and controls and verbal assent was obtained from children.

Data collection and ALL diagnosis

Two different questionnaires were used. Both questionnaires asked mothers whether the child was ever fed breast milk or milk formula and the duration of each, as well as the age when the child began receiving solid foods. Both collected data on maternal age, education, smoking, parity, newborn's weight and length, gestational age at

birth and maternal and paternal race and ethnicity. Mothers of ALL cases (n = 142) and TCCC-based controls (n = 109) completed the Texas Children's Cancer Center questionnaire at enrollment. Trained interviewers administered a validated questionnaire to mothers of NCS-based controls (n = 175). With respect to infant feeding variables, the TCCC and NCS questionnaires contained similarly structured questions regarding breast and formula feeding (closed "ever/never" questions followed by open-ended duration questions). Diagnosis of ALL (ICD-O-3 codes 9831-9837) was abstracted from the diagnostic pathology report by the research coordinator and reviewed by a medical oncologist.

Data from the TCCC and NCS questionnaires were merged for this analysis. When necessary, continuous variables were recoded categorically. Although the NCS questionnaire collected data on the ages at which children were fed breast milk and formula, the TCCC questionnaire did not. Therefore, durations of formula feeding is reported in months without respect to child's age at initiation. It is reasonable to assume that if only breastfed or only bottle fed, then the age started was at birth. In the mixed feeding group, the exact age started formula feeding is not known, but again breastfeeding was presumed to have been initiated at birth. Children were classified as exclusively breastfed if the mother indicated the child was never fed milk formula on a daily basis, and as exclusively formula fed if the mother indicated the child had never been fed breast milk on a daily basis. Children who had been fed both on a daily basis at any time were classified as mixed feeding. Age at the introduction of solids was given in months for cases and both sets of controls. Due to small numbers in racial groups such as

Asian and Native American, race was classified as either white, African American or other and ethnicity was either Hispanic or non-Hispanic.

Statistics

The statistical analysis was conducted in two phases. In the first phase of the analysis, differences in the proportions of cases and controls by infant feeding practice as well as by gestational age at birth, gender, ethnicity, maternal smoking and maternal education were assessed by Chi-square test. Differences by case-control status in the means of age at interview, birth weight, age at the introduction of solids and durations of breast and formula feeding, respectively were assessed by the Student's T-test.

In the second phase of the analysis, odds ratios (OR) and 95% confidence intervals (CI) for ALL were calculated using unconditional multiple logistic regression analysis. The main exposure variable was infant feeding group with the reference category of exclusive breast feeding, while the dependent variable was a diagnosis of ALL. In the first model, the children who were ever formula fed were compared to those exclusively breast fed; in the second model, children who were exclusively fed formula or fed both breast milk and formula were compared to the exclusively breast fed. A final set of models addressed the effects of each additional month of breastfeeding and of formula feeding and age at the introduction of solid foods on the odds ratio of ALL both individually and unadjusted, and simultaneously after adjustment for selected covariates: gender, race, ethnicity, birth weight categorized into low (< 2500 g), normal (2500-4000 g) and high (> 4000 g), child's age in years and whether the mother smoked during the

pregnancy. Statistical significance was set at $P < 0.05$ for bivariate statistics. All procedures were computed using SPSS© version 20.

IRB approval

This study was approved by the Institutional Review Boards of the University of Texas at Austin (IRB# 2012-05-0029) and Baylor College of Medicine (IRB# H-29892).

RESULTS

Table 3.1 lists the characteristics of the study population. Cases and controls ranged in age from 0 – 14 years, with means of 4.10 and 4.05 years respectively (median 3 years for both cases and controls). There were no significant differences with respect to birth weight, gestation length, gender, ethnicity or maternal education. When race was categorized into white, African American and other, there were significantly more cases than controls in the other category ($P < 0.01$). A higher proportion of cases than controls were born to mothers who smoked during pregnancy ($P < 0.001$); and among the mothers who reported smoking during pregnancy, mothers of ALL cases smoked more heavily ($P < 0.02$).

Table 3.1 Demographics and birth characteristics of ALL patients and controls

	Cases (n = 142)	**Controls (n = 284)**
	mean ± standard deviation	
Age at interview (y)	4.1 ± 2.97	4.04 ± 3.08
Birth weight (g)	3335 ± 583	3237 ± 608
	(%)	
Term length		
< 38 weeks	20.4	19.1
≥ 38 weeks[1]	73.2	77.5
Gender		
Male	52.8	51.8
Female	47.2	48.2
Race		
White	82.4	83.8
African-American	8.5	13.4
Other	9.1	2.8*
Ethnicity		
Hispanic	43.7	52.1
Non-Hispanic	55.6	47.9
Maternal smoking		
during pregnancy	8.5	3.2**
pre-pregnancy	19.7	29.6
Maternal education		
Less than high school	12.7	17.3
High school or GED	23.9	18.0
Vocational or some college	23.9	28.5
College	25.4	17.6
Graduate/Professional	14.1	18.0

*$p < 0.01$ by X^2 test, ** $p < 0.001$ by X^2 test

[1]< 1% of children in the sample were ≥ 42 weeks gestational age at birth

There were no significant differences in the percentage of cases vs. controls who were ever breast or bottle fed, nor by exclusive breastfeeding or mixed feeding (Table 3.2). There were no significant differences in the length of breastfeeding between cases and controls. Compared to cases, controls had a shorter mean duration of formula feeding; this difference was significant among the children fed both breast milk and formula ($P < 0.001$) but not among the children fed formula exclusively. The mean age at the introduction of solid foods was later among ever breastfed cases than controls ($P < 0.001$) and ever formula fed cases than controls ($P < 0.001$). There was no difference among the mean age at the introduction of solids among the exclusively breastfed or the exclusively formula fed by case-control status. Age at the introduction of solids among a group that merged both the exclusively breastfed and exclusively formula fed, that is "any exclusive feeding pattern" was significantly later among cases than controls (8.75 ± 4.12 months and 7.56 ± 3.09 respectively) ($p=0.050$). This would suggest that differences in the age at introduction of solids are persistent among cases and controls regardless of infant feeding pattern.

Table 3.2 Mean duration of infant feeding practices and age at introduction to solids among cases and controls

	Sample Size	Breastfeeding duration (mean ± standard deviation)		Formula feeding duration (mean ± standard deviation)		Age at introduction to solids (mean ± standard deviation)	
	Case/Control	Cases	Controls	Cases	Controls	Cases	Controls
Ever breastfed	108 / 201	6.54 ± 6.61	7.04 ± 5.91	-	-	8.68 ± 4.05	7.07 ± 3.32
Exclusively breastfed	16 / 36	14.47 ± 7.21	16.21 ± 5.60	-	-	9.19 ± 3.64	8.22 ± 2.72
Ever formula fed	126 / 246	-	-	**10.54 ± 4.09**	**8.09 ± 5.67***	**8.56 ± 4.18**	**6.99 ± 3.33***
Exclusively formula fed	33 / 84	-	-	12.46 ± 3.85	11.85 ± 2.82	8.52 ± 4.40	7.30 ± 3.21
Mixed feeding	92 / 161	5.32 ± 5.45	5.50 ± 4.38	9.99 ± 4.03	6.16 ± 5.79	**8.58 ± 4.13**	**6.83 ± 3.39***

* $p < 0.001$ by Student's t test

Results from the multivariable logistic regression analysis are shown in Table 3.3. The crude OR of ALL did not differ by ever formula feeding, mixed breast and bottle feeding or exclusive breastfeeding or bottle feeding. When infant feeding variables were analyzed continuously, each additional month of milk formula feeding and each additional month of age at the time of introduction of solid foods were associated with an increased odds of ALL (OR 1.17, 95% CI 1.09-1.25 and OR 1.18, 95% CI 1.07-1.30 respectively). This was the case both before and after adjustment for simultaneous effects of other infant feeding patterns, race, gender, ethnicity, age at diagnosis/interview, birthweight category and maternal smoking during pregnancy. Results were unchanged when cases and controls aged < 1 year were excluded (data not shown). Duration of breastfeeding was not significantly associated with the OR of ALL. Each 100 g increase in birthweight was associated with an 8% increase in the odds of ALL (OR 1.08, 95% CI 1.02 – 1.05). In all adjusted models there were trends towards increased odds among mothers who smoked during pregnancy and high birthweight children as well as decreased odds among African Americans, although these effects were not statistically significant.

Table 3.3 Multivariable logistic regression models for the odds ratio and 95% confidence interval of ALL by infant feeding practices and selected covariates.

	Odds ratio ((95% confidence interval)		
	Unadjusted	Adjusted[2]	Adjusted[3]
Crude[1]			
Ever fed formula	1.18 (0.63 – 2.20)	-	1.54 (0.79 – 3.01)
By practices[1]			
Exclusively formula fed	0.95 (0.47 – 1.93)	-	1.30 (0.60 – 2.80)
Mixed feeding	1.31 (0.69 – 2.48)	-	1.64 (0.83 – 3.24)
By duration			
Per additional month of breastfeeding	0.99 (0.95 – 1.03)	1.03 (0.97 – 1.09)	1.01 (0.94 – 1.08)
Per additional month of formula feeding	**1.10 (1.05 – 1.15)****	**1.16 (1.09 – 1.23)****	**1.17 (1.09 – 1.25)****
Per additional month of age at introduction of solids	**1.12 (1.06 – 1.19)****	**1.13 (1.03 – 1.26)***	**1.18 (1.07 – 1.30)***

[1] Exclusively breastfed infants serve as the referent group
[2] Adjusted for other infant feeding variables
[3] Adjusted for race, age at interview, sex, ethnicity, maternal smoking during pregnancy and birthweight category (< 2500 g 'low', 2500-3999 g 'normal', ≥ 4000 g 'high)
* $p < 0.05$, ** $p < 0.001$

DISCUSSION

In this study of 142 ALL cases aged ≤ 14 years at diagnosis, the duration of milk formula feeding and age at introduction of solid foods were found to increase the odds of ALL. In contrast, the results do not support the hypothesis that breastfeeding is protective of ALL.

Duration of infant feeding patterns appear to be more influential in predicting ALL than whether a particular pattern (e.g. mixed feeding, exclusive breast or bottle) was practiced. The findings remained after adjustment for previously identified risk factors such as race, sex, ethnicity, birthweight and gestational age at birth, maternal education and maternal smoking during pregnancy. The median age at diagnosis of 3 years was comparable to the SEER-reported peak incidence at ages 2-3[119].

The possible association of milk formula feeding and leukemia has not been well studied. In the context of recent publications reporting higher serum IGF-1 and greater growth velocity among cow's milk and cow's milk formula fed infants and children than breastfed infants and children[19,20,23,28,36], our findings may represent the identification of a novel risk factor for pediatric ALL. It has been known for some time that IGF-1 signaling is involved in the proliferation of lymphoid progenitor cells and that elevated IGF-1 may result in accelerated proliferation in these cell populations[61,110]. A case-control study which reported higher serum IGF-1 among ALL cases aged 1-11 than their controls provides partial support for this hypothesis[66]. It is possible formula feeding may promote the disease process in those with an oncogene or pre-existing epigenetic

vulnerability such as the loss of tumor-suppressor gene activity frequently observed in childhood leukemia[120-123]. Which particular genetic or epigenetic events may be sensitive to formula feeding is not currently known.

The technology of infant formulas has advanced since their inception and formula compositions have changed. Although data were not collected by type of milk formula, it is important to note there would be heterogeneity among formulas with regard to their composition across the study period. Recently, some formula manufacturers have begun to supplement their products with probiotics, although findings regarding their effects are mixed[124]. The inclusion of probiotics in infant formula was rare prior to c. 2007-2008[125,126]. The case children included in these analyses were all born prior to the advent of commonly available probiotic-containing formulas so it is unlikely the secular trend in probiotic formulas influences the results. Nonetheless, data on the specific preparation of infant formula will be important for future research. This is the first study to report an increased OR associated with each additional month of age at the introduction of solids. The mean age at introduction of solids was later among ever breastfed cases, ever formula fed cases and mixed fed cases than their respective controls. Duration of formula feeding was longer among cases than controls in the ever formula fed and mixed fed groups, whereas there was no difference in the duration of breastfeeding among mixed fed cases and their controls. Therefore, it is reasonable to assume that these cases had a higher cumulative exposure to formula. The increased OR reported for each month of age at the introduction of solids may be a result of higher cumulative exposure to formula, although these terms were independent of one another in multivariable models

and were significantly but weakly correlated (Pearson's $r = 0.129$, $p = 0.02$). It has also been shown that infant feeding practices influence the composition of the gut microbiome[127], and could thus potentially interact with the systemic immune system.

With respect to ALL, considerably more literature exists on the association of breastfeeding and breastfeeding duration and ALL risk. The American Academy of Pediatrics recommends exclusive breastfeeding through the first 6 months of life, and continuation of breastfeeding for the first year or beyond while complementary foods are introduced[44]. Results from prior studies are mixed; in many studies[128-133] but not all[134-138], breastfeeding length greater than 6 or 12 months has been observed as protective. The null finding reported here should be interpreted with caution as an effect of breastfeeding is more often detected in larger studies and meta-analyses than in studies of this approximate size. Further, the high percentage of children who ever breastfed coupled with the low percentage who were exclusively breastfed may have limited the power to detect an effect in this population. Much of the previous research on breastfeeding and ALL has been in the realm of immunology, wherein breastfeeding is considered a mediator of a healthy immune response per the Greaves Hypothesis[139]. This hypothesis may be most applicable to pre-B cell and B cell ALL and tends to weaken when all ALL subtypes or acute myeloid leukemia are considered. However, ALL was not histologically subtyped in our protocol. Lastly, among populations in which breastfeeding is promoted, the possibility of maternal over-reporting as a socially desirable response exists.

The remainder of our findings was not statistically significant. It is noteworthy however that we reported a statistically non-significant increased odds of ALL among those with high birthweight and those born to mothers who smoked during the pregnancy as well as decreased odds among the low birth weight and African-American groups which are all consistent with other studies[112,140,141]. The finding that either high birth weight in absolute terms or large for gestational age both increase risk has been reported by members of our group and others[114,134,137,141] and is hypothesized to stem from increased IGF-1 exposure *in utero*[60,142] [43, 44]. Therefore, prolonged formula feeding may recapitulate this established fetal risk factor.

This paper has several strengths; first is its novel hypothesis. Second, this analysis uses healthy, population-based controls matched on several important demographic characteristics. Both cases and controls were recruited from urban areas in a relatively narrow geographical area (central Texas) instead of the country-wide recruitment sometimes required to accrue cases, minimizing potential for confounding by geography and population density. It also heavily represents Hispanics, a rapidly growing section of the population routinely underrepresented in childhood cancer research despite being at high risk for ALL[143,144]. Finally, ours is the first study to report an association between age at the introduction of solid foods and ALL.

There are limitations to this study; because no measurement of IGF-1 accompanies the infant feeding data, any relationship of IGF-1 to the reported association between duration of formula feeding and risk of ALL remains speculative, based on extrapolation from known risk factors and prior research. We were also unable to

determine the precise ages of children when they were mixed breast and formula-fed. The importance of the ages at which a child first and last receives milk formula are therefore unknown. If a child continues to receive cow's milk after milk formula is stopped, and both increase bioavailable IGF-1, it may be that the relevant exposure is the age at which the child is first exposed to milk or milk formula, rather than simple duration. Serum IGF-1 levels vary by age in early life and there is the potential that a "critical window" exists during which infant feeding may have the strongest impact on risk. Additionally, the low percentage of exclusively breastfed children precluded analysis of the role of breastfeeding in ALL. Importantly, this study incorporates data from two populations of controls who were each interviewed using a different questionnaire. In a sensitivity analysis conducted on a subset of cases (n = 109) and only those controls who provided data using the same questionnaire as cases (n = 109), the significant multivariable regression results were essentially unchanged. Each increasing month of age at the introduction of solid food remained a statistically significant risk factor for ALL (OR 1.18, 95% CI 1.03 – 1.36) and the odds of disease for each additional month of formula feeding (OR 1.11, 95% CI 0.98 – 1.26) fell within the confidence interval of the larger model when adjusted for the same covariates. Finally, although cases were not histologically grouped for analysis, the effect of elevated IGF-1 on cell proliferation is common to B and T cell precursors[61] and should not unduly impact the results.

Future research should focus on obtaining more detailed information related to the timeline of infant feeding exposures. Since formula feeding is proposed to be

leukemogenic only in children with a predisposition, it would also be informative to stratify risk by histologic subtype, cytogenetics, or epigenetic profile to determine which factors, if any, elevate risk when coupled with prolonged formula feeding. Previous research suggests that ALLs involving high hyperdiploidy or t(1;19) translocations are more strongly associated with increasing birthweight[141] although these results are not reported universally[145]. Documenting an association between prolonged formula feeding and these subtypes of ALL may indicate a shared mechanism. Recent work has also identified added fats as risk factors for pediatric ALL[146]. It is not known whether milk formula as a whole or one of its constituents may be responsible for the findings we report.

CONCLUSIONS

This paper identifies milk formula feeding and later age at the introduction of solid foods as novel potential risk factors for pediatric ALL. Existing research on the relationship between formula feeding and serum IGF-1 in early life and the role of IGF-1 in leukemogenesis may explain the association of formula feeding with risk of ALL. Increasing age at the introduction of solid foods may be an independent risk factor or may stem from the observation that the same children who received longer formula feeding began solid foods later. Because these infant feeding practices are modifiable exposures, their putative roles in the disease process warrant further study.

Chapter 4: Identification of Vulnerable Ages for the Introduction of Solid Foods in Pediatric Acute Lymphoblastic Leukemia

ABSTRACT

There is little research concerning infant formula or age at introduction to solid foods and pediatric acute lymphoblastic leukemia (ALL). The purpose of this case-control study was to estimate the association of age at introduction of solids and pediatric ALL. 171 ALL cases aged 0-14 years were recruited at Texas Children's Cancer Center and matched on sex, age and ethnicity to 342 population-based controls. Data were collected on infant feeding and known risk factors for ALL. Multivariable logistic regression was used to model the odds ratio of ALL by quartile of age at introduction of solids with the first/earliest quartile (0-4 months) as the reference group. In adjusted models, the odds ratio of ALL among children in quartile 3 (7-9 months) was 4.08, 95% CI 1.42 – 11.71; for children in quartile 4 (≥ 10 months) the OR was 6.03, 95% CI 2.06 – 17.72. For each additional month of milk formula feeding the OR of ALL was 1.16, 95% CI 1.08 – 1.25. These results suggest a window when later introduction to solids is positively associated with ALL and recommend compliance with American Academy of Pediatrics guidelines.

INTRODUCTION

The epidemiology of pediatric acute lymphoblastic leukemia (ALL) is poorly understood. There are few recognized risk factors, such as Down syndrome and exposure to ionizing radiation, which account for a small percentage of cases[147]. ALL patients often harbor one of a suite of genetic or epigenetic lesions linked to the disease; however, not all diagnoses are driven by these and not all children with an oncogenic mutation will develop leukemia[147]. Early life immune exposures likely play a role in the etiology of ALL[148]. Evidence suggests that either an overall lack of immune challenges or an inappropriate response to them by the immune system may be a risk factor for childhood ALL[149]. One marker of immune exposure, breast feeding, has been associated with lower ALL risk, specifically breast feeding for a duration of > 6 months[116]. Duration of breast feeding is only one component of infant feeding, however.

Breastmilk, milk formula and the introduction of solid foods stimulate the infant digestive and immune systems. Breast feeding transfers antibodies, antigens and human milk oligosaccharides from mother to offspring[150]. Breastfed infants experience slower weight gain and have, on average, lower serum insulin-like growth factor-1 (IGF-1) levels than cow's milk formula-fed infants[15,23]. IGF-1 has been reported to have antiapoptotic effects on lymphoid progenitor cells *in vitro*[61]. Our prior work identified a higher odds of ALL for each additional month of age at the introduction of solid foods and for longer duration of milk formula feeding[109] when these were modeled continuously.

The objectives of the current analysis were to examine the associations of age at introduction to solid foods and durations of breast feeding and milk formula feeding with the odds of ALL. We sought to investigate the specific age or age range past which introduction of solids is associated with the increased risk of ALL. We hypothesized that

later introduction of solid foods is associated with an increased odds of ALL. We also sought to explore whether the effect of later introduction of solids is different among children without an older sibling, which serves as an indicator for limited infectious exposures in early life.

MATERIALS AND METHODS

Subjects

This case-control study included 171 cases of childhood ALL (ICD-O-3 codes 9831-9837) aged 0-14 years who were diagnosed at Texas Children's Cancer Center (TCCC) in Houston, Texas from 1997-2012 and had complete exposure data. Parents of 116 cases responded to the questionnaire at the time of diagnosis. For 55 cases, parents responded to the questionnaire after the end of induction therapy. Median time between diagnosis and completion of the questionnaire in this group was 6.01 years. Maximum time between diagnosis and interview in this group was 13.3 years. 342 population-based controls recruited from Austin, Houston and San Antonio, Texas were frequency matched to cases on sex, ethnicity (Hispanic or not) and age within 1 year at diagnosis/interview. Parents of cases and controls reported sociodemographic and maternal reproductive data as well as the duration of breast feeding, milk formula feeding and the age at introduction of solids during an interviewer-administered questionnaire. Assessment was comparable between cases and controls. Cases and controls with the following characteristics were excluded from the analysis: diagnosis of a genetic condition associated with childhood cancer; diagnosis of an inherited metabolic disease that might affect infant feeding; the parent/guardian was unable to provide information on infant feeding practices; the index child was currently breastfed, fed milk formula or had not been introduced to solids.

The parent/guardian provided written informed consent for participation while the child provided verbal assent, if at the age of assent. This study was approved by the Institutional Review Boards of the University of Texas at Austin and Baylor College of Medicine and was conducted in accord with the principles of the Declaration of Helsinki.

Statistics

Differences in the means of continuous variables among cases and controls were assessed using Student's t-test or Mann-Whitney U test. Differences in the proportions of categorical variables were assessed using χ^2 tests or likelihood ratio tests, as appropriate. Continuous data are presented as means with standard deviations or as medians with interquartile ranges, when non-normally distributed.

Unconditional multivariable logistic regression was used to model the odds ratio (OR) and 95% confidence interval (CI) of ALL by duration of breast feeding, duration of milk formula feeding and age at introduction to solid foods. Race/ethnicity, age at diagnosis/interview, birthweight, number of older siblings and maternal smoking status during pregnancy were included as covariates. Because of sample size, the effects of race and ethnicity are reported only for Hispanic white, non-Hispanic white and non-Hispanic black children. Duration of breast feeding and milk formula feeding were treated as continuous variables reported in months. Age at introduction to solid foods was categorized as 0-4 months, 5-6 months, 7-9 months and 10 or more months. The American Academy of Pediatrics recommends exclusive breast feeding for 6 months[44]. We wished to compare the effects of introducing solids earlier than, at, or later than 6 months. The univariate OR and 95% CI were first calculated for each independent variable. Any variable significantly associated with the outcome was included in an initial final model. A backward elimination procedure was used to select the most

parsimonious multivariable model. We initially included maternal education and maternal pre-pregnancy smoking but found no direct effect and no evidence of confounding by these variables, so they were excluded from the final model. There were no significant interactions between independent variables. Missing covariate data was handled via pairwise deletion. To test whether these findings were affected by the presence of the 55 cases enrolled as survivors, we then computed the same model using only the cases whose parent or guardian responded to the questionnaire at the time of diagnosis.

Because of the hypothesis that the introduction of solid foods to an infant or child may act as an immune exposure, we then computed the multiple logistic regression models separately among children with and without one or more older siblings. Having older siblings has been used as a surrogate marker of immune exposures such as common infections[149].

For all tests, a P-value of ≤ 0.05 was considered statistically significant. All analyses were conducted in IBM SPSS© version 21.

IRB approval

This study was approved by the Institutional Review Boards of the University of Texas at Austin (IRB# 2012-05-0029) and Baylor College of Medicine (IRB# H-29892).

RESULTS

Tables 4.1 and 4.2 list characteristics of cases and controls as well as infant feeding practices and age at introduction to solid foods. There were no significant differences between cases and controls by age at diagnosis/interview, sex, ethnicity, proportion of children with at least one older sibling or number of older siblings. Cases were more likely than controls to be of unknown race or of Asian, American Indian or

Middle Eastern descent. Mothers of cases were more likely to have report smoking during the index pregnancy than were mothers of controls. Mean birthweight was higher among cases than controls. The median duration of milk formula feeding was longer among cases than controls. The median age at introduction to solid food was later among cases than controls. A lower proportion of cases than controls were introduced to solid foods at 5-6 months whereas higher proportions of cases than controls were introduced to solid foods between 7-9 months and ≥ 10 months.

Table 4.1 Characteristics of cases and controls

	Cases (n=171)	Controls (n=342)	P-value[1]
Age at diagnosis/interview ($\bar{x}$ ± s.d.)	4.4 ± 3.1	4.1 ± 3.3	0.34
Percent male (n)	53.2 (91)	52.6 (180)	0.90
Percent female (n)	46.8 (80)	47.4 (162)	
Race, % (n)			
Percent White (n)	85.4 (146)	86.3 (295)	
Percent Black (n)	7.0 (12)	10.5 (36)	**0.05**
Percent Other[2] (n)	7.6 (13)	3.2 (11)	
Ethnicity			
Percent Hispanic (n)	49.1 (84)	55.0 (188)	0.21
Percent Non-Hispanic (n)	50.9 (87)	45.0 (154)	
Birthweight ($\bar{x}$ ± s.d.)	3381 ± 588	3265 ± 603	**0.04**
Percent firstborn (n)	52.7 (77)	58.1 (182)	0.28
Number of older siblings ($\bar{x}$ ± s.d.)	0.8 ± 1.0	1.0 ±1.2	0.10
Maternal smoking in pregnancy			
Percent reporting 'yes' (n)	8.9 (15)	3.3 (11)	**<0.01**

[1] Test for significant difference between cases and controls

[2] Includes person of American Indian (n=3 cases, 0 controls), Asian (n=5 cases, 7 controls), mixed (n=1 case, 4 controls) and unknown (n=4 cases, 0 controls) descent.

Table 4.2 Infant feeding practices by case-control status

	Cases (n=171)	Controls (n=342)	P-value[1]
Percent ever breastfed (n)	76.0 (130)	72.2 (247)	0.36
Breastfeeding duration, months (median ± IQR)	3.5 ± 4.0	5.0 ± 7.0	0.07
Percent ever formula fed (n)	89.5 (153)	85.3 (291)	0.19
Formula feeding, months (median ± IQR)	12.0 ± 4.0	7.0 ± 12.0	**<0.001**
Age at introduction to solids, months (median ± IQR)	8.0 ±4.0	6.0 ± 4.0	**<0.001**
Solids at ≤ 4 months % (n)	13.3 (21)	19.2 (61)	
Solids at 5-6 months % (n)	24.7 (39)	43.4 (138)	**<0.001**
Solids at 7-9 months % (n)	28.5 (45)	18.2 (58)	
Solids at ≥ 10 months % (n)	33.5 (53)	19.2 (61)	

[1] Test for significant difference between cases and controls

Results of unconditional logistic regression models for the OR and 95% CI of ALL by age at introduction to solids, infant feeding practices and covariates are presented in Table 4.3. In univariate models, the OR of ALL was significantly elevated among children who began solid foods at 7-9 months or ≥ 10 months as well as with each additional month of milk formula feeding (P for linear trend < 0.001). The ORs of ALL were lower among Hispanic white compared to non-Hispanic white children but higher among children of mothers who smoked during pregnancy and with increasing birthweight of the index child.

Table 4.3 Multivariable logistic regression models for the OR and 95% CI of ALL by age at introduction to solids

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Race/ethnicity		
Non-Hispanic white	1.00	1.00
Hispanic white	**0.63 (0.42-0.94)**	0.61 (0.30-1.25)
Non-Hispanic black	0.49 (0.23-1.02)	0.28 (0.08-1.05)
Sex		
Female	1.00	1.00
Male	1.03 (0.71-1.48)	1.08 (0.56-2.08)
Maternal smoking during pregnancy		
No	1.00	1.00
Yes	**2.87 (1.29-6.39)**	2.91 (0.55-15.32)
Birthweight (per 100g increase)	**1.03 (1.00-1.07)**	**1.06 (1.00-1.13)**
Older siblings		
None	1.00	1.00
1 or more	0.80 (0.54-1.19)	0.87 (0.46-1.64)
Breastfeeding (per additional month)	0.99 (0.96-1.02)	0.99 (0.93-1.06)
Milk formula feeding (per additional month)	**1.07 (1.03-1.11)**	**1.16 (1.08-1.25)**
Age at introduction to solids		
0-4 months	1.00	1.00
5-6 months	0.82 (0.45-1.51)	1.11 (0.40-3.16)
7-9 months	**2.25 (1.20—4.23)**	**4.08 (1.42-11.71)**
10 or more months	**2.52 (1.36-4.68)**	**6.03 (2.06-17.72)**

Age at introduction to solids remained the strongest risk factor for ALL in the adjusted multivariable model. The OR of ALL was significantly higher among children introduced to solid foods at 7-9 or ≥ 10 months of age (P for linear trend < 0.001). Each additional month of milk formula feeding was positively associated with OR of ALL. No differences in the OR of ALL persisted by race/ethnicity or maternal smoking in pregnancy; however, increasing birthweight (per 100g) remained positively associated with the OR of ALL.

Results of the sensitivity analysis omitting survivors are given in table 4.4. In the adjusted model, the OR of ALL among Hispanic white compared to non-Hispanic white children was significantly decreased, in contrast to the model using the full dataset. Duration of milk formula feeding and introduction to solid foods at ≥ 7 months of age remained positively associated with the OR of ALL.

Table 4.4 Multivariable logistic regression models for the OR and 95% CI of ALL by age at introduction to solids among incident cases

	Adjusted OR[1] (95% CI)
Race/ethnicity	
Non-Hispanic white	1.00
Hispanic white	**0.51 (0.28 – 0.92)**
Non-Hispanic black	0.54 (0.19 – 1.41)
Sex	
Female	1.00
Male	0.90 (0.52 – 1.54)
Maternal smoking during pregnancy	
No	1.00
Yes	1.15 (0.22 – 4.85)
Birthweight (per 100g increase)	1.03 (0.98 – 1.08)
Older siblings	
None	1.00
1 or more	0.80 (0.47 – 1.35)
Breastfeeding (per additional month)	1.03 (0.98 – 1.08)
Milk formula feeding (per additional month)	**1.11 (1.04 – 1.18)**
Age at introduction to solids	
0-4 months	1.00
5-6 months	1.02 (0.43 – 2.61)
7-9 months	**3.59 (1.54 - 9.04)**
10 or more months	**3.91 (1.64 – 10.10)**

[1] adjusted for all listed variables

When logistic regression models were stratified according to whether the child had at least 1 older sibling, the effect of later introduction to solid foods was only significant among children without an older sibling. Considering children without an older sibling (n=94 cases, 160 controls) the OR of ALL per additional month of age at the introduction of solids was 1.20 (95% CI 1.03 – 1.39, data not shown). Among children with at least one older sibling, there was no significant increase in the OR according to age at introduction to solids (quartile 3, OR = 3.08, 95% CI = 0.72 – 13.18; quartile 4 OR = 3.13, 95% CI = 0.73 – 13.38). Stratification by presence of an older sibling had no effect on the OR per additional month of milk formula feeding.

DISCUSSION

Our results suggest that children introduced to solid foods at 7 months or later are at increased odds of pediatric ALL after adjustment for covariates. In stratified analyses, this effect was significant only among children without an older sibling. Increasing duration of milk formula feeding and higher birthweight were also significantly associated with ALL, although their effects were smaller. The effect of duration of milk formula feeding was unchanged when stratified by sibship status.

Research regarding the effect of age at introduction to solid foods and childhood diet are mixed. A recent study reported no effect of introducing solids > 4 months on childhood ALL, but noted a significant increase in the OR for childhood brain tumors[151]. This discrepancy may be due to differences in study populations or in the cut-off for ages,

as there was similarly no increase in the odds of ALL among children introduced to solids at or before 6 months in our analysis. An emerging body of evidence suggests that infant diet effects the maturation of the gut and oral microbiomes and the early immune system[152-155]; thus breastmilk and solid foods may represent immune challenges and may have age-specific effects. Our finding that age at introduction to solids was a stronger risk factor among children without an older sibling suggests the possibility of effect modification by other immune exposures. While both ours and the Australian study[151] adjusted for child's birth order the available data did not permit us to assess the effect of other markers of immune stimulation such as daycare attendance or early infections, leaving open the possibility of residual confounding.

Prior research has reported both high birthweight[2,3,5] and milk formula feeding[68,109,151] to be associated with pediatric ALL. Two studies examined the association between ALL and the ages at which children were fed formula. MacArthur et al. reported an increased odds of ALL among children who received more than 50% of their diet from a milk supplement at 7-12 months of age[68], while Greenop et al. reported increased odds of ALL among children who began receiving cow's milk formula within the first 14 days or who were exclusively formula fed for the first 6 months[151]. Mean serum IGF-1 levels are lower among breastfed than milk formula-fed infants[19], and high birthweight is considered a marker of greater IGF-1 exposure *in utero*[60]. IGF-1 induces the proliferation of lymphoid progenitor cells *in vitro*[61] and is the proposed mechanism for the consistent associations of high birthweight and large-for-gestational age with ALL[60]. When our analysis was stratified by presence of an older sibling the effect of

duration of milk formula feeding remained significant in both groups, suggesting that duration of milk formula feeding may work through a different mechanism than timing of introduction of solids. Our findings of a positive association between birthweight and the odds of ALL are consistent with the literature[2,3,5].

One strength of this study is its representation of Hispanic children. Recent analysis of Surveillance, Epidemiology and End Results Program data suggest that the proportion of ALL cases who are of Hispanic ethnicity is increasing. At the same time, the 5-year ALL mortality hazard ratio among Hispanic children compared to non-Hispanic white children increased over the previous decade[156]. Future studies of pediatric ALL must include Hispanic populations in order to address this inequality.

Secondly, whereas much previous research has been limited to the effect of any breast feeding this study additionally accounts for the effects of formula and solid foods. We are the first to report that the effect of infant diet may depend on whether the child encounters other immune exposures in early life. On the basis of evidence that an infant's diet affects the development of the microbiome and the maturation of the immune system[152-155] we attempted to adjust for the child's likelihood of acquiring other immune exposures. Birth order, number of siblings and daycare attendance are commonly used as markers of immune exposures in studies of pediatric ALL[149]. Because infants and children with older siblings may receive exposure to infective agents through siblings which firstborn or only children would not, they may benefit from additional protection against ALL[148]. Therefore, we hypothesized that the potential immunogenic effect of introduction of solid foods would be reduced in such children as their immune

systems are more likely to face concurrent challenges. The observed data are consistent with this hypothesis.

A limitation of the current analysis is that the data did not permit calculation of the duration of exclusive breast feeding according to the World Health Organization (WHO) definition. Further, data on the specific solid foods first introduced were not available. The WHO recommends maintaining breast feeding after six months of age as complementary foods are introduced. Our findings are consistent with this recommendation. Another limitation is that using whether a child has an older sibling as a surrogate marker of immune exposures is imperfect[149]. Presence of an older sibling was chosen because it was not feasible to directly assess history of infections due to the sparseness of this data in our sample. Finally, wide confidence intervals for the upper categories of age at introduction to solids in the analysis stratified by older siblings reflect the small numbers of children in these groups. Further research based on a greater sample size is needed to confirm these results and provide more precise estimates of these effects.

CONCLUSIONS

These findings suggest that infants who were introduced to solids later than 6 months of age were at increased odds of childhood ALL. Importantly, this effect may be stronger among children who are absent other markers of immune exposure. Further exploration of the vulnerable period in infancy related to the types of solid foods, other

markers of immune exposure and the mechanisms underlying their effects during the second half of infancy is warranted.

ACKNOWLEDGEMENTS

The authors would like to thank all study participants for their contribution to the published research. There are no funding sources or conflicts of interest to disclose. This work was conducted at Baylor College of Medicine and the University of Texas at Austin.

Chapter 5: The Relationships of Childhood Height and Weight to Pediatric Acute Lymphoblastic Leukemia

ABSTRACT

Greater exposure to insulin-like growth factor 1 (IGF-1) is a putative risk factor for pediatric acute lymphoblastic leukemia (ALL). Height at diagnosis, a marker of IGF-1 exposure, has been tested in connection with ALL. Most prior studies have compared cases to national reference data derived from earlier birth cohorts. Our objective was to determine the association of height-for-age Z score (HAZ) at time of diagnosis with the OR of ALL using a case-control design (N=498) with a contemporaneous population of age- sex- and ethnicity-matched controls. We hypothesized that cases would have greater mean HAZ at time of diagnosis/interview, after adjustment for weight-for-age (WAZ) and weight-for-height (WHZ). HAZ was not associated with ALL. For each one standard deviation increase in WAZ the OR of ALL was 0.83 (95% CI 0.68 – 0.99). The OR of ALL was increased among children with either a WAZ $\leq$ -2 (OR 5.10, 95% CI 1.85 – 16.75) or WHZ of $\leq$ -2 (OR 5.27, 95% CI 1.65 – 23.61). Previous findings of taller height among ALL cases may arise from the choice of control populations. Children with low WAZ or WHZ were at increased odds of ALL; these findings may reflect acute malnutrition due to disease.

INTRODUCTION

Growth hormone (GH) and somatomedins have been proposed to play a role in the etiology of pediatric acute lymphoblastic leukemia (ALL). Repeated findings of higher mean birthweight among ALL cases as compared to controls co-occur with higher mean cord blood insulin-like growth factor 1 (IGF-1) levels in infants and therefore support the hypothesis that children with higher levels of GH or somatomedins are at greater risk of ALL[3-5,60]. IGF-1 and GH directly related to stature[20,157]. This has led some to test the hypothesis that children diagnosed with ALL are taller than their peers[158-166]. Higher birthweight or taller height at diagnosis may reflect greater early life exposure to GH and IGF-1[60].

Studies of height and ALL most commonly compare the heights or age-adjusted heights of ALL cases to either national reference data for childhood growth[158-161,165,166] or to an internal control group selected from the same source population as cases[163,164]. Results from these studies are mixed; some have reported that ALL cases are taller than expected[158-160,165,166] whereas others report null associations[161-164]. These discrepancies may be explained at least in part by the differences in the referent group for cases. Both studies using an internal control group reported no relationship between height and ALL[163,164]. Among six studies which compared cases to reference data[158-161,165,166] five reported a positive association between height and ALL[158-160,165,166]. National reference data are updated periodically but may still include older birth cohort data and not reflect norms for birth cohorts from which the cases are recruited. In the United States, for

example, growth references were last updated in 2000 although some of the data on which these norms are based were collected prior to 1980[167]. Due to a secular trend towards increased height in the population[168], a potential methodological weakness of studies which compare incident ALL cases to national reference data is that any finding of taller height among cases may reflect a general trend towards increased height in the population over time, rather than a biological association of height with disease. Because of this, further studies of height and ALL using cases and matched controls are required.

Early life GH and IGF-1 levels may also affect weight in children. Greater intake of energy and protein in infancy and childhood is associated with higher total and bioavailable IGF-1 levels[19,20,35,36] and with greater body mass[7,9,19]. Therefore, age- or height-adjusted weight may also be useful as a marker of GH and IGF-1 exposure and could be expected to share the putative etiological role of height in leukemogenesis. Indeed, Suminoe et. al. reported a significantly higher proportion of ALL cases with body weight 2 or more standard deviations above the mean at time of diagnosis[166]. Despite this, associations of weight-for-age and weight-for-height with ALL risk are less studied than height-for-age. We wished to adjust for the effects of weight when testing for an association of height with ALL. We also wanted to determine whether weight-for-age or weight-for-height are associated with ALL risk independent of height-for-age. Whether these factors are associated with ALL is of interest in populations with high rates of pediatric overweight and obesity[169].

The objective of this study was to determine whether there is an association between height-for-age Z score (HAZ) at time of diagnosis and the OR of ALL using a contemporaneous population of controls drawn from the same population during the same years. We hypothesized that ALL cases would be taller than controls (have a higher mean HAZ) at time of diagnosis/interview and that increasing HAZ would be positively associated with the OR of ALL in logistic regression models. We also tested whether weight-for-age Z score (WAZ) and weight-for-height Z score (WHZ) were associated with the OR of ALL independently of HAZ.

MATERIALS AND METHODS

Subjects

Among 255 ALL cases diagnosed between 1997 and 2015 at Texas Children's Hospital, 249 children and adolescents ≤ 14 years of age were included in this study; thereby excluding six cases age 15 and older. The 249 cases were frequency matched to 249 population-based controls (total N=498) on sex, ethnicity and age at diagnosis/interview. Controls were recruited between June 2008 and January 2014. Parents of cases and controls provided data on race, ethnicity, parental educational attainment and child's birthweight, sex and age at diagnosis/interview. Race was classified as white, black or other. Ethnicity was classified as Hispanic or non-Hispanic. Maternal education was classified as less than high school, high school or GED or post-high school, which included trade or technical school, college, and post-graduate education. Height (in cm) and weight (in kg) at diagnosis were abstracted from medical

records for cases. When height and/or weight had been measured multiple times, the measurement taken on the date closest to the date of diagnosis was used. Trained interviewers recorded height and weight among controls at the time of entry into the study.

Statistics

HAZ and WAZ scores were computed from the Centers for Disease Control and Prevention (CDC) 2000 growth charts using the LMS (lambda-mu-sigma) method detailed on their website[170]. This method produces a Z-score using the given physical measurement (X), the median for that age and sex (M), the generalized coefficient of variation (S) and the power in the Box-Cox transformation (L) according to the following formulas:

$$Z = \frac{\left(\left(\frac{X}{M}\right)^{L}\right)-1}{LS}, L \neq 0 \text{ or } Z = \frac{\ln\left(\frac{X}{M}\right)}{S}, L = 0$$

Weight-for-length Z scores were computed for children less than 3 years of age and for recumbent length measurements 45 – 103.5 cm. Weight-for-stature Z scores were computed for children ages 3 years and older who had a measured height between 77 and 121.5 cm. 356 children (188 cases and 168 controls) met these criteria. Hereafter, we refer to weight-for-length and weight-for-stature collectively as weight-for-height (WHZ).

Chi-squared tests were used to test for differences in the proportions of sex, race, ethnicity and maternal education by case-control status. The distributions of HAZ, WAZ and WHZ among cases and controls were visually examined using density plots. The two-sample Kolmogorov-Smirnov test with Bonferroni-Holm correction was used to test for differences in the distributions of HAZ, WAZ and WHZ by case-control status. Analysis of variance with Bonferroni-Holm post-hoc correction was used to test for differences in mean HAZ, WAZ and WHZ between cases and controls overall and within the age categories 0-4 years and 5 or more years.

Univariate and then multiple logistic regression analysis were computed to estimate the odds ratio (OR) of ALL according to HAZ, WAZ and WHZ and then after adjustment for sociodemographic covariates. First, single variable models for the OR of ALL based on HAZ, WAZ and WHZ were computed. Two adjusted models were then created, one which contained HAZ and WHZ and another which contained WAZ and HAZ. Both included maternal education and race/ethnicity as covariates. These same models were then computed with anthropometric Z scores reported as three-level categorical variables ($\leq$ -2, -1.99 – 1.99, $\geq$ 2). Statistical analysis was conducted in R version 3.2.5 and RStudio version 0.98.939. Density plots were generated using the ggplot2 package[171].

IRB approval

This study was approved by the Institutional Review Boards of the University of Texas at Austin (IRB# 2012-05-0029) and Baylor College of Medicine (IRB# H-29892).

RESULTS

Table 5.1 lists sociodemographic characteristics of cases and controls. A higher proportion of cases than controls were white whereas a lower proportion was black. There were no differences by sex, ethnicity, age at diagnosis/interview or maternal education between cases and controls.

Table 5.1 Characteristics of cases and controls

Participant Characteristics	Cases N (%)	Controls N (%)	P-value
Total	249	249	
Sex			
Male	137 (55.0%)	137 (55.0%)	1.00
Female	112 (45.0%)	112 (45.0%)	
Age at diagnosis/interview			
<5 years	106 (42.6%)	114 (45.8%)	0.53
5 years or older	143 (57.4%)	135 (54.2%)	
Race			
White	223 (89.9%)	184 (73.9%)	< 0.01
Black	14 (5.6%)	54 (21.7%)	
Other	11 (4.4%)	11 (4.4%)	
Ethnicity			
Non-Hispanic	110 (44.2%)	120 (48.2%)	0.42
Hispanic	139 (55.8%)	129 (51.8%)	
Mother's Education			
Less than High School	36 (14.8%)	36 (14.7%)	
High School or GED	57 (23.4%)	54 (22.0%)	0.94
Post High School	151 (61.9%)	155 (63.3%)	
Not Specified	5 (2.0%)	4 (1.61%)	

Table 5.2 shows the means and standard deviations for HAZ, WAZ and WHZ among cases and controls overall and by age category. There were no differences in mean HAZ between cases and controls. Considering the entire study sample, cases had lower mean WAZ and WHZ scores than did controls. Lower mean WAZ among cases was also evident among children aged 5 or older.

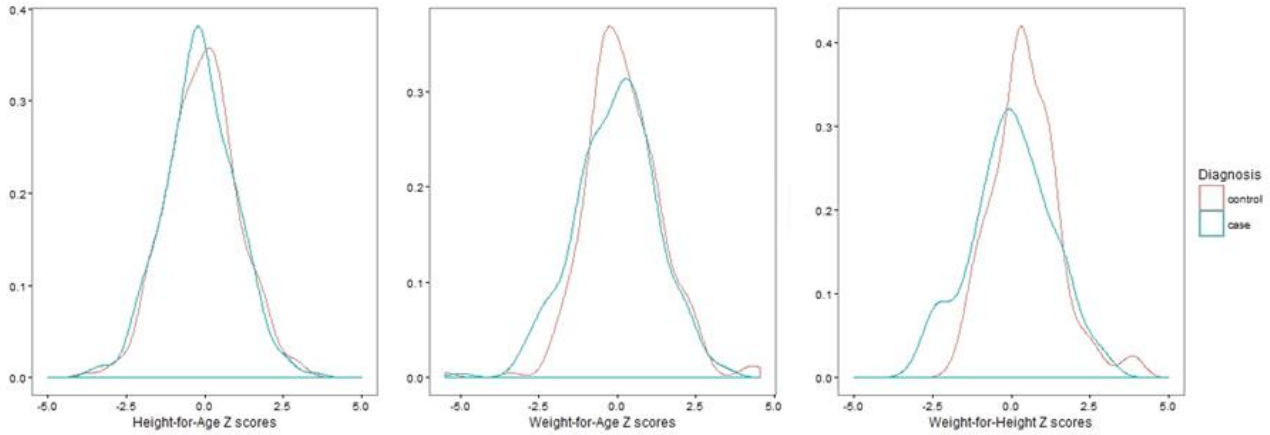
Table 5.2 Height-for-Age, Weight-for-Age and Weight-for-Height Z scores (Mean ± SD) of cases and controls

Participant Characteristics	Mean Z-Score (SD)		
	Cases	Controls	P-value*
Height-for-Age Z-Score			
Overall	-0.16 (1.13)	-0.10 (1.26)	0.62
<5 years	-0.22 (1.16)	-0.42 (1.24)	0.31
5 years or older	-0.05 (1.09)	0.28 (1.08)	0.09
Weight-For-Age Z-Score			
Overall	**-0.05 (1.30)**	**0.20 (1.21)**	**0.03**
<5 years	-0.14 (1.28)	-0.09 (1.27)	0.74
5 years or older	**0.08 (1.33)**	**0.53 (1.04)**	**0.03**
Weight-For-Height Z-Score			
Overall	**0.02 (1.29)**	**0.36 (1.99)**	**0.05**
<5 years	0.05 (1.29)	0.32 (2.20)	0.71
5 years or older	-0.08 (1.33)	0.50 (0.91)	0.70

*Post-hoc ANOVA comparisons use the Bonferroni-Holm correction for multiple testing

Figure 5.1 provides density plots for the distributions of HAZ, WAZ and WHZ among cases and controls. After adjustment for multiple comparisons, there was a significant difference in the distribution of WHZ by case-control status ($p < 0.005$).

Figure 5.1 Distributions of Height-for-Age, Weight-for-Age and Weight-for-Height Z scores among cases (blue) and controls (red)



Tables 5.3 and 5.4 present results of multivariable logistic regression models for the adjusted OR of ALL. In adjusted models the continuous parameterizations of HAZ and WHZ were not associated with the OR of ALL (5.3A & 5.3B). WAZ was negatively associated with the OR of ALL. When anthropometrics were analyzed categorically, the OR of ALL was elevated among children with WAZ or WHZ $\leq$ -2 (5.4A & 5.4B). A consistently reduced OR of ALL was observed across all models when comparing black to white children.

Table 5.3 Multivariable logistic regression models of Height-for-Age and Weight-for-Height Z scores on the odds ratio of ALL

	Adjusted OR (95% CI)
Height-for-age Z score	1.03 (0.85 – 1.26)
Weight-for-height Z score	0.89 (0.77 – 1.03)
Race	
White	1.00
Black	**0.26 (0.11 – 0.56)**
Other	0.86 (0.26 – 3.06)
Ethnicity	
Non-Hispanic	1.00
Hispanic	0.64 (0.39 – 1.06)
Maternal Education	
Post high school	1.00
High School or GED	1.26 (0.72 – 2.21)
Less than high school	1.16 (0.62 – 2.18)

Table 5.4 Multivariable logistic regression models of Height-for-Age and Weight-for-Age Z scores on the odds ratio of ALL

	Adjusted OR (95% CI)
Height-for-age Z score	1.10 (0.90 – 1.35)
Weight-for-age Z score	**0.83 (0.68 – 0.99)**
Race	
White	1.00
Black	**0.18 (0.09 – 0.35)**
Other	0.72 (0.45 – 1.07)
Ethnicity	
Non-Hispanic	1.00
Hispanic	0.69 (0.45 – 1.07)
Maternal Education	
Post high school	1.00
High school or GED	1.10 (0.69 – 1.77)
Less than high school	0.99 (0.57 – 1.72)

Table 5.5 Multivariable logistic regression models of Height-for-Age and Weight-for-Height category on the odds ratio of ALL

	Adjusted OR (95% CI)
Height-for-age Z score	
≤ -2	1.34 (0.53 – 3.50)
-1.99 – 1.99	1.00
≥ 2	1.85 (0.36 – 13.58)
Weight-for-height Z score	
≤ -2	**5.27 (1.65 – 23.61)**
-1.99 – 1.99	1.00
≥ 2	0.91 (0.39 – 2.12)
Race	
White	1.00
Black	**0.23 (0.10 – 0.52)**
Other	0.69 (0.19 – 2.58)
Ethnicity	
Non-Hispanic	1.00
Hispanic	0.61 (0.36 – 1.01)
Maternal Education	
Post high school	1.00
High School or GED	1.24 (0.70 – 2.19)
Less than high school	1.16 (0.62 – 2.19)

Table 5.6 Multivariable logistic regression models of Height-for-Age and Weight-for-Age category on the odds ratio of ALL

	Adjusted OR (95% CI)
Height-for-age Z score	
≤ -2	1.09 (0.42 – 2.92)
-1.99 – 1.99	1.00
≥ 2	0.68 (0.21 – 2.12)
Weight-for-age Z score	
≤ -2	**5.10 (1.85 – 16.75)**
-1.99 – 1.99	1.00
≥ 2	1.20 (0.57 – 2.56)
Race	
White	1.00
Black	**0.16 (0.08 – 0.32)**
Other	0.73 (0.29 – 1.85)
Ethnicity	
Non-Hispanic	1.00
Hispanic	0.67 (0.43 – 1.05)
Maternal Education	
Post high school	1.00
High school or GED	1.09 (0.68 – 1.75)
Less than high school	0.96 (0.55 – 1.69)

DISCUSSION

In this study of pediatric ALL cases and age-matched population-based controls, no association was observed between HAZ and the OR of ALL. Some studies have reported taller height among ALL cases than controls[158-160,165,166] whereas others have not[161-164]. This inconsistency may be due to the use of different comparison groups in these studies. Two of the studies used internal controls recruited specifically for the study from the same underlying population rather than reference data; both reported no association of height with ALL[163,164]. Six of the studies[158-161,165,166] did not have an internal control group, instead comparing ALL cases to national reference data. Five of these six reported a positive association of height with ALL[158-160,165,166]. Davis et. al. reported that male cases were 0.67 cm taller on average and female cases were 0.30 cm taller on average than the population norm. Huang et. al. reported that cases had a mean height z score of 0.29 (compared to a population mean of 0.00), equivalent on average to a 1.32 cm difference in height between cases and population norms. A potential issue with this approach is whether the reference data were contemporaneous with the ages of the cases and therefore the time period for case ascertainment. For example, Broomhall et. al. compared cases diagnosed in 1972-73 to reference data from the 1950's, while Huang et. al. compared cases diagnosed between 1988-2007 to values from the CDC 2000 growth charts, which are based partially on data collected before 1980[167]. From 1960-2002 the United States experienced an increase in mean height of 2.03 cm among boys ages 6-11 and an increase in mean height of 1.5 cm among girls ages 6-11[168]. The magnitude of this change exceeds the mean difference in height between ALL cases and the total population of U.S. children reported by Huang et. al, for example[160]. It is possible therefore that studies which compare cases to older population values/birth

cohorts may report taller height among cases due to the secular trend in increased height in the population over time rather than any true relationship between height and disease. Two studies used reference data collected during the same years as case recruitment and reported positive associations between height and ALL[159,166] suggesting that validity of reference data may not wholly explain the associations reported by other studies using this methodology. Our data, consistent with those of other studies using age-matched contemporaneous controls, do not support the hypothesis that children with ALL are taller than the populations/birth cohorts from which they were drawn.

We examined the effects of WAZ and WHZ on the OR of ALL. Visual analysis of the distributions of WAZ and WHZ indicated higher proportions of cases than controls with Z scores < -2, a recognized cut-off for wasting[172]. This was confirmed by the lower mean WAZ among cases than controls overall and in the subgroup aged 5 years or older as well as the lower mean WHZ among cases than controls overall. In the multiple logistic regression models, the OR of ALL decreased by 17% for each 1 standard deviation increase in WAZ and the OR was higher among children with WAZ or WHZ ≤ -2. Malnourishment among a subset of cases has been noted at approximately the same frequency in other studies of ALL as in ours (5-10% of cases) and likely reflects the disease process, as the absence of any deficit in HAZ suggests the absence of chronic malnutrition[172,173]. Although elevated, the ORs reported for WAZ and WHZ ≤ -2 should be interpreted with caution as few children fell into these categories. In this analysis, 26 children (21 cases and 5 controls) were found to have WAZ ≤ -2 whereas 19 children (16 cases and 3 controls) were found to have WHZ ≤ -2. The importance of low WAZ and WHZ as prognostic markers is unclear, with some studies reporting similar overall and event-free survival in these children compared with those having WAZ or WHZ > -2[174] and others reporting poorer outcomes in malnourished children[172].

All four logistic regression models show a significantly decreased OR of ALL among African-Americans compared to whites, which is consistent with national data. In contrast to the majority of published data, we also report non-significantly decreased ORs of ALL among Hispanics compared to non-Hispanics[175]. We find no association of ALL with maternal education, which we included as a marker of socioeconomic status.

The greatest strength of this study is the use of an age-matched control group largely recruited during the same time period, reducing potential confounding arising from comparing cases to reference data which may have been collected 20 years or more prior to the ALL cases. The use of measured height improves the accuracy of exposure assessment and limits recall bias which arises in case-control studies from differential self-report of exposures by parents or guardians of cases and controls. 53% of the study sample was Hispanic; Hispanics are the largest growing segment of the U.S. population and are at a higher risk of ALL[175]. Therefore this study has the potential to help understand the etiology of ALL in this group, who can be expected to represent an increased proportion of ALL cases in the U.S. moving forward. Finally, this study adjusted for child's WAZ and WHZ when reporting the effect of height-for-age on the OR of ALL. The majority of studies to date have not considered weight when reporting the effects of height.

The lack of longitudinal data on WAZ and WHZ makes it difficult to determine whether the lower mean WAZ and WHZ among cases at the time of diagnosis reflects differential weight gain in childhood or acute malnourishment arising from the disease. These findings are presumed to reflect acute changes in nutritional status secondary to disease onset. However, if in fact they are not acute in nature then a small portion of ALL cases may display a pattern of low weight gain for a period of time prior to the onset of disease. The small numbers of children with Z-scores below -2 leads to imprecise

estimates of effect size. Finally, we computed anthropometric Z scores for both cases and controls from the CDC 2000 growth data for children in the United States. As mentioned previously, these data are based in part on data collected in previous generations of children. This could potentially inflate mean z scores in our study sample if the average height and weight of children are increasing over time. However, this applies both to cases and controls, so case-control comparisons should be unbiased by any change in mean of HAZ, WAZ and WHZ.

CONCLUSIONS

This study does not support the hypothesis that ALL cases at diagnosis are taller than age-matched controls. Findings of a positive association between height and ALL primarily arise from studies which compare cases to reference data rather than to age-matched controls. We report a negative association of weight-for-age Z-score with the OR of ALL and higher ORs of ALL among children with either WAZ or WHZ-scores $\leq$ -2 which are likely the result of a portion of ALL cases experiencing acute malnutrition at the time of diagnosis.

Chapter 6: Conclusions

This research examined the effects of infant and childhood diet on thelarche at 10.8 and 12.9 years and serum IGF-1 levels at 10.8 years in healthy girls, as well as the associations of infant feeding practices with the OR of pediatric ALL. We report associations of thelarche with childhood dairy consumption, child's weight and maternal overweight and of ALL with longer duration of milk formula feeding and later age at introduction to solid foods.

INFANT FEEDING PATTERNS, CHILDHOOD DIET AND PUBERTAL DEVELOPMENT IN GIRLS

Chapter 2 discusses the effects of *in utero* PE exposure, infant feeding practices and diet from 3-5 years on IGF-1 levels and anthropometrics at 10.8 and 12.9 years in Norwegian girls. We observed several differences in birth characteristics between infants exposed to PE *in utero* compared to those not exposed which are consistent with the literature[57,71,85]. Infants exposed to PE *in utero* had shorter mean gestational length, lower mean cord blood IGF-1 levels and lower mean birthweight and length. PE mothers were younger than NT mothers.

Tanner breast stage was strongly positively related to serum IGF-1 levels at follow-up, with girls having more advanced breast development also having higher serum IGF-1 levels. Specifically, compared to Tanner 1 girls, mean serum IGF-1 was 20.9% higher for Tanner 2 girls, 48.1% higher among Tanner 3 girls and 132.8% higher among Tanner 4 girls. Taller children also had higher serum IGF-1 levels. Neither PE exposure *in utero* nor dietary intake were associated with serum IGF-1 at follow-up. Although higher intakes of milk, milk formula and animal protein are associated with higher serum IGF-1 levels in infants and young children, there is a suspected negative association between serum IGF-1 levels in childhood and adulthood. One study demonstrated lower

serum IGF-1 levels among adults who had received supplemental milk as children. serum IGF-1 levels among adults who had received supplemental milk during childhood[45]. Greater weight gain during infancy predict higher adiposity in childhood and adulthood[7,43]. These data suggest that early life diet is involved in developmental programming of body composition and serum IGF-1 levels. The relationships of infant feeding practices to serum IGF-1 in older children and adolescents are not well studied. This study does not provide evidence for these associations.

Child's weight and maternal overweight were positively associated and frequency of dairy consumption was negatively associated with the OR of thelarche at 10.8 years. This is consistent with prior studies, which have identified earlier onset of puberty among heavier girls[46,176-178]. In our sample, frequency of dairy consumption was significantly associated with a reduced OR of thelarche at 10.8 years and non-significantly negatively associated with weight. These data suggest dairy consumption in childhood may reduce BMI in adolescent girls, leading to a lower proportion of girls having undergone thelarche at 10.8 years. At 12.9 years, only current weight and height were associated with more advanced breast development, defined as Tanner breast stage 3 or above after adjustment for covariates.

This research provides limited evidence that breastfeeding may modify the associations of PE exposure *in utero* and childhood diet with thelarche at 10.8 years. PE exposure *in utero* was associated with a reduced OR of thelarche among exclusively breastfed girls. Conversely, childhood frequency of dairy consumption was not associated with the OR of thelarche. There is evidence in the literature for effect modification of *in utero* exposures by breastfeeding status. One study found methylation levels at the gene H19 were higher among children born $\geq 85^{th}$ percentile of birthweight-for-gestational age, and that H19 higher methylation was associated with the risk of

overweight or obesity at 1 year. Breastfeeding attenuated birthweight-associated changes in H19 methylation fraction and breastfed children were not at increased risk of overweight or obesity according to H19 methylation[98]. Replication studies will be required to determine whether our findings are reflective of effect modification by breastfeeding status.

INFANT FEEDING PATTERNS, CHILDHOOD ANTHROPOMETRICS AND PEDIATRIC ALL

Chapters 3 & 4 examined the effects of infant feeding practices on pediatric ALL. The OR of ALL is increased among children who received milk formula feeding longer (OR per each additional month of milk formula feeding 1.17, 95% CI 1.09 – 1.25). These data support the hypothesis that longer duration of milk formula feeding increases the risk of ALL, which was developed on the basis of evidence that milk formula feeding increases serum IGF-1 levels in children and does not provide an equivalent stimulus for the development of the immune system as breastmilk. The OR of ALL is also increased among children introduced to solid foods later (OR per each additional month of age at the introduction of solids 1.18, 95% CI 1.07 – 1.30)[109]. Both higher IGF-1 exposure and delayed immune exposures are believed to increase risk of pediatric ALL[60,139].

We next sought to identify whether there were critical ages for the introduction of solid foods in pediatric ALL. Children introduced to solid foods at either 7 months of age or later were at increased odds of ALL compared to children introduced at ≤ 6 months of age. There was a significant linear trend towards increasing OR of ALL with increasing age at introduction to solids. Children introduced at ≥ 10 months of age were at the highest odds of ALL (OR of ALL 6.03, 95% CI 2.06 – 17.72 as compared to children introduced to solids at 0-4 months). Although the sample size (n = 171 cases, 342 controls) does not allow for precise estimates of the OR of ALL for children

introduced in each quartile, these data provide evidence that delayed introduction of solids increases the risk of ALL.

Finally, we used height and weight at time of diagnosis as proximal markers of IGF-1 exposure in children. We tested the hypothesis that children diagnosed with ALL would be taller than their healthy peers. Findings regarding the association of height at diagnosis with ALL risk are mixed, possibly owing to inconsistent study designs. We compared the age- and sex- adjusted heights of cases to age- and sex- matched contemporaneous controls and reported no association of height at diagnosis with ALL after adjustment for weight-for-age or weight-for-height plus covariates. Mean WAZ was lower among ALL cases and the OR of ALL was inversely associated with weight-for-age Z score (OR per 1-unit increase in WAZ 0.83, 95% CI 0.68 – 0.99).

There are inherent difficulties involved in using height at diagnosis as a surrogate for infant feeding exposures. Any effect of infant feeding practices on height at time of diagnosis may be obscured by more proximal nutritional exposures and health status, particularly in older children. Height is also a heritable trait and it is possible that genetic factors which determine height are the same as or co-vary with genetic traits that determine ALL risk. Because taller height is an indicator of greater IGF-1 exposure, the lack of a positive association between height and ALL may also indicate the lack of involvement of IGF-1 in determining ALL risk. This explanation is less likely given the extensive body of research indicating both mechanistic and epidemiologic linkages between IGF-1 and leukemogenesis.

PUBLIC HEALTH IMPLICATIONS

This research was conducted to explore the effects of infant and childhood diet on health and disease outcomes. These data provide evidence that infant and childhood diet

affect pubertal development and risk of multiple non-communicable diseases throughout the life course.

Childhood dairy consumption from 3-5 years was associated with reduced OR of thelarche in girls at 10.8 years. Earlier age at onset of puberty in girls increases lifetime risk of breast cancer, which is the most common non-cutaneous cancer among women in the United States[52]. Small changes in mean age at onset of puberty in girls would result in practically important changes in the burden of breast cancer in the total population[179]. We report a non-significant negative relationship of frequency of dairy intake from 3-5 years and weight at follow-up, which has previously been noted in both pediatric[180] and adult populations[181]. This association may be explained by the negative correlation of dairy consumption with sugar-sweetened beverage consumption[182,183]. Given that increased child and maternal weight were associated with breast development at 10.8 years and more advanced breast development at 12.9 years it is possible that increased childhood dairy consumption acts to decrease the likelihood of breast development at 10.8 years by reducing bodyweight and adiposity in children. Hence, interventions designed to increase dairy intake in children and adolescents have the potential to decrease bodyweight. Such changes would likely be reflected in reduced incidence of chronic disease during adulthood, specifically cancer, diabetes and cardiovascular disease.

Infant feeding practices were associated with the OR of pediatric ALL. ALL is the most common pediatric cancer in the United States[52]. The Centers for Disease Control estimates approximately 4,000 new cases of ALL will be diagnosed in children and adolescents in 2016. In contrast with most other pediatric cancers, the incidence rate of ALL is increasing[175]. This parallels the rising incidence of other pediatric conditions related to diet and immunity, for example type 1 diabetes[184] and food allergies and likely

reflects changes in early life exposures over the last several decades[184-186]. Additionally, it is known that Hispanic children are at a higher risk of ALL as compared to non-Hispanic white children[187]. Therefore the increase in ALL incidence may also reflect the higher proportion of Hispanics in the U.S. population over this time. Although 5-year survival rates among children aged 1-14 are high relative to other cancers ALL survivors are at increased risk of a number of late effects over the life course as a result of treatment. These include increased risk of a second malignant neoplasm or cardiovascular disease, overweight and obesity and reduced intelligence quotient[188-193]. These statistics suggest the burdens of ALL incidence and survivorship will increase in the years to come and recommend research focused on improving our understanding of ALL etiology and prevention.

Duration of formula feeding and timing of introduction to solids are strong candidates for ALL prevention efforts. Many risk factors for ALL are genetic or non-modifiable. Infant feeding practices are among the most comprehensively researched non-genetic risk factors for ALL and there is already considerable interest in improving breastfeeding rates among mothers for prevention of childhood overweight and obesity, necrotizing enterocolitis in premature infants and common childhood infections[44]. While a majority of Hispanic mothers initiate breastfeeding, they demonstrate shorter mean breastfeeding duration compared to non-Hispanic whites and are more likely to provide formula in addition to breastmilk[11,194,195]. Increasing breastfeeding duration and decreasing formula feeding duration among Hispanic mother-infant dyads may reduce ALL incidence in this already at-risk population.

In summary, this research provides evidence that infant and childhood diet are associated with ALL in childhood and breast cancer and cardiovascular disease in adulthood. Seminal studies of children born during the Dutch Hunger Winter as well as

more recent longitudinal studies of diet and growth during infancy and childhood suggest that lifetime risk of many non-communicable diseases is established during early life. Infant and childhood diet are modifiable risk factors in the prevention of pediatric ALL and chronic diseases.

FUTURE DIRECTIONS

Future work in infant feeding and ALL aims to 1) robustly estimate the effects of duration of formula feeding (modeling exclusive formula feeding separately from mixed breast- and formula-feeding) and age at introduction to solid foods in a pooled analysis of infant feeding data from multiple study sites to enhance statistical power and 2) to use metagenomics and metabolomics to identify putative molecular mechanisms for infant feeding-ALL associations. There is mounting evidence to demonstrate that infant diet affects development of the gut microbiome and systemic immune system. However, the gut microbiome has not been studied in connection with ALL. I will conduct this work as the Cancer Prevention Research Institute of Texas molecular epidemiology postdoctoral fellow at Baylor College of Medicine (BCM).

The gut microbiome, immune system and risk of ALL

Breastmilk contains bioactive compounds such as immunoglobulin A (IgA) and a variety of human milk oligosaccharides (HMOs), the most abundant of which is 2'-fucosyllactose (2'-FL). These compounds affect antibacterial and antimicrobial activity in the gut and oral cavity of infants and are the primary determinant of the infant's gut

microbiome. Evidence from animal models suggests that HMOs and commensal intestinal bacteria are involved in the development of the infant's immune system.

Breastmilk is a vector for the transfer of immunogenic compounds from mother to infant. In neonates, IgA secreted in breastmilk plays a critical role in facilitating normal immune responses among infants[196]. Breastmilk supports the activity of xanthine oxidase and lactoperoxidase, two key antimicrobial enzymes in the oral cavity of infants. In the presence of breastmilk these enzymes produce hydrogen peroxide at concentrations which are adequate to inhibit the growth of pathogenic bacteria such as *Staphylococcus aureus* and *Salmonella spp*[155]. It is also known that the relative abundances of bacteria in the infant intestine differ between breastfed and formula-fed infants. The greater carbohydrate content and presence of HMOs in breastmilk are associated with a gut microbiome which is more diverse and is enriched for *Bifidobacteria*[197-199]. Acetate produced by *Bifidobacteria* as an end-product of carbohydrate metabolism has been shown to inhibit growth of *Escherichia coli* and to prevent death in *E. coli* 0157 infected mice[200].

While breastmilk and commensal bacteria bolster immune response in neonates, there is mounting evidence that they also participate in developmental programming of the immune system. This is manifested both directly, through the interactions of HMOs in peripheral blood with immune cells as well as indirectly through interactions of the mucosal immune system with commensal bacteria. Goehring et. al. identified multiple HMOs including 2'-FL in urine and plasma of breastfed but not formula-fed infants using gas chromatography/mass spectrometry[201] indicating that these molecules are absorbed

into the infant's bloodstream. Lymphocytes isolated from piglets and cultured *ex vivo* with HMOs show a number of differences from cells unexposed to HMOs. These include oligosaccharide-specific effects on T-cell proliferation; lower T-helper cell counts and greater cytotoxic T-cell counts among HMO-exposed cells in response to challenge with lipopolysaccharide; and increased interleukin-10 production among HMO-exposed cells[153].

Short-chain fatty acids and other metabolites derived from the microbiome have been proposed to regulate development of the infant immune system through an epigenetic mechanism, with breastfed infants showing greater expression of genes involved in the development of immunity[202,203]. Infants with higher stool abundance of *Bifidobacteria* also show more robust immune responses[204] and infant feeding patterns have been associated with natural killer cell and T-cell counts[152]. Finally, breastfed rhesus macaques showed more robust correlation networks between T-cell subsets during the juvenile period (3-5 years) than never-breastfed animals[205], suggesting that relationships between infant feeding patterns and immune cell activation may persist at least into adolescence. As an infant is weaned the diversity of the microbiome increases and shifts towards that of an adult; this process is believed to be complete by approximately 3 years of age. Greater microbial diversity results in immune development as the infant is exposed to a wider array of antigens[206].

Abnormal early development of the immune system is believed to be a key event in the natural history of pediatric ALL[53]. Although certain oncogenic gene fusions are recurrently identified in pediatric ALL cases, some cases do not harbor any identifiable

genetic risk factors and many children with these mutations will not develop ALL[53,207]. It is believed that ALL arises in at-risk children whose immune systems do not develop appropriately, commonly as a result of delayed immune exposures (a "two-hit" model)[139]. These findings support a potential IGF-1 independent relationship of infant diet with ALL risk – reduced stimulation of the immune system and lower diversity of the gut microbiome among infants who are formula-fed or introduced to solid foods later, resulting in a less robust immune system during early life.

I propose to collect infant feeding data and stool samples on incident ALL cases and healthy controls through 3 years of age (at which point the gut microbiome is more like that of an adult)[208]. I will then characterize how the gut microbiome and metabolome differ among cases and controls; and whether infant feeding patterns affect microbial diversity and microbial metabolites uniquely among cases v. controls. Bacterial diversity will be characterized using 16s rRNA sequencing. We will interrogate the metagenomes and blood metabolomes of cases and controls for differences in bacterial activity and metabolites. Detection of changes to the gut microbiomes of ALL cases and controls by type and duration of formula feeding and also by age at/delayed introduction of solids will be used to identify putative ALL-associated changes in the microbiome. This will accelerate understanding of ALL etiology and aid in cancer prevention since infant feeding practices and early diet are highly modifiable behaviors.

In another phase of my postdoctoral studies, I propose to undertake a longitudinal study of the blood metabolome of ALL cases pre- and post-induction therapy to identify

compounds that predict treatment response. This information will then be used to improve current risk stratification and treatment algorithms in pediatric ALL.

Dr. James Versalovic of the Texas Children's Microbiome Center and Dr. Michael Scheurer will serve as mentors for this research. Dr. Scheurer, Dr. Michele Forman and I have collaboratively designed an infant feeding questionnaire which is already in use at BCM and provides the exposure data required for this research. The infant feeding questionnaire was validated as part of the National Children's Study Formative Research led by Dr. Forman and the CDC Infant Feeding Practices II Study (Appendix B).

Pooled analysis of infant feeding data

Working with Dr. Scheurer and Dr. Forman I have also proposed a pooled analysis of infant feeding data through the Childhood Leukemia International Consortium (CLIC). Under the supervision of Dr. Scheurer, who is a CLIC member, and Dr. Forman I will conduct a pooled analysis of infant feeding data from CLIC study sites. The goal of this research is to determine the effects of duration of any breastfeeding and exclusive breastfeeding, duration of any formula feeding and exclusive formula feeding and age at introduction to solid foods on the risk of pediatric ALL. This research will produce robust estimates of the effects of duration of simultaneous breast and formula feeding as compared to exclusive formula feeding and exclusive breast feeding on the risk of ALL by pooling infant feeding data from multiple study centers to increase sample size and precision in the magnitude of effect. It will also be the first such study to separately

estimate the risk of ALL according to exclusive as compared to mixed breast and formula feeding. I hypothesize that longer duration of formula feeding will be associated with an increased OR of ALL and that this effect will be greater in the exclusively formula fed than the breastfed or breast- and formula-fed children. Regarding solid foods, I hypothesize that older age at time of introduction to solid foods will be associated with an increased OR of ALL. This research has the potential to identify whether there is a dose-response relationship between formula feeding and risk of ALL and in conjunction with analysis of the responses of the case and control microbiomes to infant feeding practices identify putative molecular mechanisms for these associations. The results may strengthen the evidence for longer duration of formula feeding and later introduction to solid foods as risk factors for pediatric ALL and aid in cancer prevention efforts by identifying modifiable risk factors.

Appendix A: Case-Control Consent Form

CONSENT FORM HIPAA Compliant

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Case subjects

H-19264- EXPLORING POTENTIAL RISK FACTORS FOR CHILDHOOD CANCER AND HEMATOLOGICAL DISORDERS BY CASE-CONTROL STUDIES

Background

In this form the term "you" signifies either you or your child, and the term "we" signifies the investigators.

This research will be conducted at the Texas Children's Cancer Center and Childhood Cancer Epidemiology and Prevention Center. All research projects that are carried out in this institution are governed by the rules of Baylor College of Medicine, Texas Children's Hospital and the Federal Government. Please ask the study investigator to explain any words or information that are not clear to you.

Before you learn about the study, it is important that you know the following: 1) Whether or not you will participate in this study is entirely up to you. 2) Even if you agree to participate, you may withdraw from the study at any time. 3) If you decide not to be in the study, or if you decide to withdraw from the study at any time, you will not lose any of your benefits (like for instance routine medical care).

Once you understand the study, and if you agree to participate to it, you will be asked to sign this consent form, and you will be given a copy of the form.

Every year approximately 12,000 to 13,000 children and adolescents are diagnosed with cancer in the U.S. In most of these cases we do not know why cancer occurred in that particular person. One way to discover possible reasons that cause cancer is to do "case-control" studies. In these studies, there are two groups of participants: one group of persons diagnosed with a cancer (namely the "case" group), and the second group that includes persons who do not have cancer (namely the "control" group). We look for factors that belong to subjects with cancer but are not present in people without cancer. The factors may lead to further research efforts to see if we can identify why cancer occurs.

This study is being done to conduct a case-control study. This means that the investigators intend to put together two groups of infants/children/adolescents who in the case group have a diagnosis of cancer, and in the control group do not have cancer. If the participant is a case, then both a blood sample and a buccal cell sample will be collected. If the participant is a control only a buccal cell sample is required. If the control participant agrees a blood sample can also be collected. However this is optional. Samples will be obtained from both groups as well as personal and family health information. The information obtained from both groups will be compared to each other. This way the investigators hope to understand better why and how cancer occurs in children. Using the information included in the questionnaire we will explore whether the following can be associated with childhood cancer: maternal and paternal exposures including infectious diseases before birth, maternal drug use before and after birth, smoking during pregnancy, medications taken during pregnancy, infections, medical illnesses, medications and other environmental exposures for the child after birth.

This research study is sponsored by Baylor College of Medicine

Patient ID _____

H-19264- EXPLORING POTENTIAL RISK FACTORS FOR CHILDHOOD CANCER AND HEMATOLOGICAL DISORDERS BY CASE-CONTROL STUDIES

Purpose
The primary purpose of this research is to identify risk factors for childhood cancer.

Procedures
A total of 4000 subjects at 7 institutions will be asked to participate in this study. You will be one of approximately 4000 subjects to be asked to participate at this location.

We feel that it is important for you to know how many people we plan to enroll on this study.

The research will be conducted at the following location(s): Baylor College of Medicine, McAllen Texas Children's Cancer Center, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, TCH: Texas Children's Hospital, Wellness Center, Texas Children's Pediatric Associates (TCPA), UT: MD Anderson Cancer Center.

If you are a case subject, and agree to participate in this research study, we will ask you to give one blood sample and a buccal cell sample.

If you are a control subject, and agree to participate in this research study, you will be asked to give a buccal cell sample only. You will also be asked to give a blood sample, however, this is OPTIONAL. You can indicate if you would like to do this or not at the end of this section with the other optional questions.

From your blood specimen, we will obtain plasma and DNA (basic building blocks in your blood cells) to conduct other studies to determine new risk factors that are found in your genes

The total amount of blood drawn will be based on your weight and age, and should not be harmful to you. We would like to obtain no more than 4 (four) teaspoons of blood (meaning 20 cc), one time during the study only. This total amount of blood drawn will be within the safety limits, and it may be less than 4 teaspoons depending on body-weight. However, no more than a total amount of 3 cc of blood (3ml, less than 1 teaspoon) per kilogram of body-weight will be drawn from children.

Collection of blood involves sticking a vein with a needle. We will avoid a separate stick, by obtaining this blood from you at the same time when another blood sample is obtained from you in the clinic or operating room. However, if you agree, a separate stick can be done just for the purpose of this research.

In addition to blood draw, a sample of your buccal cells will be obtained from you for this study. This will be done via mouthwash collection.

STUDY DURATION AND USE OF SAMPLES:
After obtaining the biological samples, and completing the questionnaire form, you will no longer be asked for any other procedure within this study.

The research specimens (blood, saliva/buccal cells) that we obtained from you may be stored for a long period of time, or indefinitely, in the laboratory of our center.

Patient ID _____

Although investigators will have a record that the blood specimen and the questionnaire were obtained from you, your identity will be kept strictly confidential. Every reasonable effort will be made at all times to maintain the confidentiality of your study records and of your research information.

If you decide that you want to withdraw from the study, then your research information and data will be entirely deleted from the study records, and your samples will be discarded. You may contact the Principal Investigator in writing with this request.

Research data obtained from the samples and the questionnaire will be compared in future case-control studies.

OPTION TO CONSENT FOR OPTIONAL ONE TIME BLOOD COLLECTION:
CONTROL PARTICIPANTS ONLY (BLOOD):
The total amount of blood drawn for the study will be no more than 4 teaspoons (20 cc). However, no more than a total amount of 3 cc (less than 1 teaspoon) per kilogram of body weight will be drawn from children.

Please indicate your option by initializing and dating just ONE of the following:

Yes, I do (initials, and date) _____

No, I do not (initials, and date) _____

consent to the collection and use of blood for this protocol.

ALL PARTICIPANTS (BUCCAL CELLS):
Buccal cells are cells from the inner lining of your mouth or cheek. These cells are routinely shed and replaced by new cells. As the old cells shed they are in your saliva and can be easily collected via a simple procedure using mouthwash. In the event that we are not able to obtain enough sample or we are not able to get DNA analysis results, you may be contacted to provide a second saliva/buccal cell sample by mail.

Please indicate your option by initializing and dating just one of the following for giving permission to us to contact you by phone or mail for this reason:

Yes, I do (initials, and date) _____

No, I do not (initials and date) _____

consent for you to contact me for an additional saliva/buccal cell sample for this protocol.

OPTION TO CONSENT FOR ADDITIONAL COLLECTION (if needed):
CASE PARTICIPANTS ONLY (BLOOD):

Patient ID _____

In the event that we are not able to draw enough blood or we do not get an adequate sample for DNA analysis results, you may be asked to provide a second sample at the time of your next visit in order to obtain the same amount of blood so that tests can be done again. If you are asked to give a second sample, the total amount of blood drawn for the study will be no more than 4 teaspoons (20 cc). However, no more than a total amount of 3 cc (less than 1 teaspoon) per kilogram of body weight will be drawn from children.

Please indicate your option by initializing and dating just ONE of the following:

Yes, I do (initials, and date) _____

No, I do not (initials, and date) _____

consent to the collection and use of additional blood for this protocol.

OPTION TO CONSENT TO BE CONTACTED TO CLARIFY ANSWERS ON QUESTIONNAIRE:
In addition, you will be asked to fill out a questionnaire, as we want to learn about your health, and about diseases that you and members of your family may have or may have had in the past. Some questions will also refer to your life style and living place, like for example smoking, air pollution and others, in order to find out more about possible causes for cancer. You may find that some questions are uncomfortable to you, or too personal, or you may just not know the answer to some of them. In such case, you may simply skip that particular question and go to the next one. The time taken to complete this questionnaire will be approximately 15-20 minutes. In rare situations we might need clarification about an answer that you provided in the questionnaire. Please let us know if we may contact you about your answers to the questionnaire by initializing below.

_____ Yes, I give permission to be contacted for clarification on my answers in the questionnaire.

_____ No, I do not give permission to be contacted for clarification on my answers in the questionnaire.

OPTION TO CONSENT TO BE CONTACTED ABOUT FUTURE RESEARCH:
In the future, new research projects may be developed based on the results of this present study and your participation to that research might be of significance. We would like to ask your permission to contact you again if we decide that your participation to that research is of relevance. The option of whether you would like or not to be recontacted for future research is entirely up to you also. Please, indicate your option by initializing below:

_____ Yes, I would like to be contacted in the future for other research.

_____ No, I do not wish to be contacted in the future for other research.

The purpose of this project is to develop new knowledge about the causes and risk factors of developing cancer in children. Because the studies we plan to do are research procedures for which

the clinical relevance has not yet been proven, we will in general not be able to provide clinical information or any results from this research to you. Conclusive results of future studies can become available to the public when they will be published in peer reviewed scientific journals. Even then, you will not be identified by name in such publications. We will notify you if we think you may be at increased risk and the discovery has been validated independently by a second study.

CONTROL GROUP OPTION TO CONSENT TO BE CONTACTED ABOUT RESULTS:
Throughout the conduct of this study we may find out that you may have an increased risk of developing cancer, although you are not ill now. A second study will be done by our group or an independent second group of investigators. Only if our findings are confirmed we will notify you. Both studies must be published or accepted to be published in peer-reviewed medical journals before we send you a notice.

This does not meanthat you have cancer, or that you will definitely develop cancer. It actually means that when we compare you to the general population, you may have an increased risk of developing a cancer in general.

If we obtain such information, we will offer you the option to receive this information individually. It is important for you to know that these will be research results only, and they must be confirmed in a clinical or diagnostic laboratory in order to be used for medical decisions. We will not track the control subjects to see if they develop cancer in the future.

If your research findings show an increased risk of cancer in general, and if you choose to receive this information, we will offer to make arrangements for you to speak to an oncologist, or to a cancer prevention counselor, to help you understand the meaning of the research results.

We will also give you information about clinical testing laboratories that provide confirmation of research results on a fee basis.

Please, let us know if you want to receive research results by checking the appropriate place below.

_____ Yes, I would like to be contacted in the future to learn the results of research studies that used my information if I am at increased risk.

_____ No, I do not wish to be contacted in the future to learn the results of research studies that used my information.

You can see and get a copy of your research related health information. Your research doctor may be able to provide you with part of your information while the study is in progress and the rest of your information at the end of the study.

Potential Risks and Discomforts
Your risks from taking part to this study are small. In the first place there may be a risk related to blood draw, and this means: possible bleeding, pain, redness, swelling or bruising at the site of needle stick. Rarely an infection may occur at the site of the needle stick. However, all these

incidents are rare. There are no additional risks related to obtaining a buccal cells sample.

Another risk may be that your blood samples and your answers to the questionnaire will be linked to your name. All reasonable efforts will be made to keep your name and identity strictly confidential throughout this study and the future studies that will utilize your information. The research data obtained from you will not be added to your medical record. Also, future publication of research results that will include information obtained from you will be anonymous.

This research involves genetic studies, and it is possible throughout the study to uncover some information regarding your chances of developing cancer. This means that we may find a risk factor that you may have, that increases your risk of getting a cancer. If you choose to be informed about this information, there is a risk of emotional distress for you.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

Potential Benefits
You will receive no direct benefit from your participation in this study. However, your participation may help the investigators better understand why cancer occurs in infants, children and adolescents. Based on the information obtained from this study, the investigators may find out about new causes that lead to cancer.

Alternatives
The following alternative procedures or treatments are available if you choose not to participate in this study: the only alternative to this study is to not participate.

Subject Costs and Payments
You will not be asked to pay any costs related to this research.

You will not be paid for taking part in this study.

Subject's Rights
Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

Patient ID _____

Your Health Information

We may be collecting health information that could be linked to you (protected health information). This protected health information might have your name, address, social security number or something else that identifies you attached to it. Federal law wants us to get your permission to use your protected health information for this study. Your signature on this form means that you give us permission to use your protected health information for this research study.

If you decide to take part in the study, your protected health information will not be given out except as allowed by law or as described in this form. Everyone working with your protected health information will work to keep this information private. The results of the data from the study may be published. However, you will not be identified by name.

People who give medical care and ensure quality from the institutions where the research is being done, the sponsor(s) listed in the sections above, representatives of the sponsor, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study. Because of the need for the investigator and study staff to release information to these parties, complete privacy cannot be guaranteed.

The people listed above will be able to access your information for as long as they need to, even after the study is completed.

If you decide to stop taking part in the study or if you are removed from the study, you may decide that you no longer allow protected health information that identifies you to be used in this research study. Contact the study staff to tell them of this decision, and they will give you an address so that you can inform the investigator in writing. The investigator will honor your decision unless not being able to use your identifiable health information would affect the safety or quality of the research study.

The investigator, MEHMET FATIH OKCU, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: MEHMET FATIH OKCU at 832-822-1511 during the day.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child's name here _____

Patient ID _____

H-19264- EXPLORING POTENTIAL RISK FACTORS FOR CHILDHOOD CANCER AND HEMATOLOGICAL DISORDERS BY CASE-CONTROL STUDIES

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Legally Authorized Representative Parent or Guardian	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date

Patient ID _____

H-19264- EXPLORING POTENTIAL RISK FACTORS FOR CHILDHOOD CANCER AND HEMATOLOGICAL DISORDERS BY CASE-CONTROL STUDIES

Background

You are invited to take part in a research study. Please read this information and feel free to ask any questions before you agree to take part in the study.

In this form the term "you" signifies either you or your child, and the term "we" signifies the investigators.

This research will be conducted at the Texas Children's Cancer Center and Childhood Cancer Epidemiology and Prevention Center. All research projects that are carried out in this institution are governed by the rules of Baylor College of Medicine, Texas Children's Hospital and the Federal Government. Please ask the study investigator to explain any words or information that are not clear to you.

Before you learn about the study, it is important that you know the following: 1) Whether or not you will participate in this study is entirely up to you. 2) Even if you agree to participate, you may withdraw from the study at any time. 3) If you decide not to be in the study, or if you decide to withdraw from the study at any time, you will not lose any of your benefits (like for instance routine medical care).

Once you understand the study, and if you agree to participate to it, you will be asked to sign this consent form, and you will be given a copy of the form.

Every year approximately 12,000 to 13,000 children and adolescents are diagnosed with cancer in the U.S. In most of these cases we do not know why cancer occurred in that particular person. One way to discover possible reasons that cause cancer is to do "case-control" studies. In these studies, there are two groups of participants: one group of persons diagnosed with a cancer (namely the "case" group), and the second group that includes persons who do not have cancer (namely the "control" group). We look for factors that belong to subjects with cancer but are not present in people without cancer. The factors may lead to further research efforts to see if we can identify why cancer occurs.

This study is being done to conduct a case-control study. This means that the investigators intend to put together two groups of infants/children/adolescents who in the case group have a diagnosis of cancer, and in the control group do not have cancer. Samples will be obtained from both groups as well as personal and family health information. The information obtained from both groups will be compared to each other. This way the investigators hope to understand better why and how cancer occurs in children. Using the information included in the questionnaire we will explore whether the following can be associated with childhood cancer: maternal and paternal exposures including infectious diseases before birth, maternal drug use before and after birth, smoking during pregnancy, medications taken during pregnancy, infections, medical illnesses, medications and other environmental exposures for the child after birth.

This research study is sponsored by Baylor College of Medicine

Patient ID _____

H-19264- EXPLORING POTENTIAL RISK FACTORS FOR CHILDHOOD CANCER AND HEMATOLOGICAL DISORDERS BY CASE-CONTROL STUDIES

Purpose
The primary purpose of this research is to identify risk factors for childhood cancer.

Procedures
A total of 4000 subjects at 7 institutions will be asked to participate in this study. You will be one of approximately 4000 subjects to be asked to participate at this location.

We feel that it is important for you to know how many people we plan to enroll on this study.

The research will be conducted at the following location(s): Baylor College of Medicine, McAllen Texas Children's Cancer Center, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, TCH: Texas Children's Hospital, Wellness Center, Texas Children's Pediatric Associates (TCPA), UT: MD Anderson Cancer Center.

As a control subject, if you agree to participate in this research study, you will be asked to give a saliva / buccal cell (mouth wash or a swipe with a cotton swab) sample only.

From your buccal cells, we will obtain DNA (basic building blocks in your blood cells) to conduct other studies to determine new risk factors that are found in your genes.

STUDY DURATION AND USE OF SAMPLES:
After obtaining the buccal cell sample and completing the questionnaire form, you will no longer be asked for any other procedure within this study.

The research specimens (saliva/buccal cells) that we obtained from you may be stored for a long period of time, or indefinitely, in the laboratory of our center.

Although investigators will have a record that the saliva/buccal cells and the questionnaire were obtained from you, your identity will be kept strictly confidential. Every reasonable effort will be made at all times to maintain the confidentiality of your study records and of your research information.

If you decide that you want to withdraw from the study, then your research information and data will be entirely deleted from the study records, and your samples will be discarded. You may contact the Principal Investigator in writing with this request.

Research data obtained from the samples and the questionnaire will be compared in future case-control studies.

CONTROL PARTICIPANTS (BUCCAL CELLS):
Buccal cells are cells from the inner lining of your mouth or cheek. These cells are routinely shed and replaced by new cells. As the old cells shed they are in your saliva and can be easily collected via a simple procedure using mouthwash. In the event that we are not able to obtain enough sample or we are not able to get DNA analysis results, you may be contacted to provide a second saliva/buccal cell sample by mail.

Patient ID _____

Please indicate your option by initializing and dating just one of the following for giving permission to us to contact you by phone or mail for this reason:

Yes, I do (initials, and date) _____

No, I do not (initials and date) _____

consent for you to contact me for an additional saliva/buccal cell sample for this protocol.

OPTION TO CONSENT TO BE CONTACTED TO CLARIFY ANSWERS ON QUESTIONNAIRE:
In addition, you will be asked to fill out a questionnaire, as we want to learn about your health, and about diseases that you and members of your family may have or may have had in the past. Some questions will also refer to your life style and living place, like for example smoking, air pollution and others, in order to find out more about possible causes for cancer. You may find that some questions are uncomfortable to you, or too personal, or you may just not know the answer to some of them. In such case, you may simply skip that particular question and go to the next one. The time taken to complete this questionnaire will be approximately 15-20 minutes. In rare situations we might need clarification about an answer that you provided in the questionnaire. Please let us know if we may contact you about your answers to the questionnaire by initializing below.

_____ Yes, I give permission to be contacted for clarification on my answers in the questionnaire.

_____ No, I do not give permission to be contacted for clarification on my answers in the questionnaire.

OPTION TO CONSENT TO BE CONTACTED ABOUT FUTURE RESEARCH:
In the future, new research projects may be developed based on the results of this present study and your participation to that research might be of significance. We would like to ask your permission to contact you again if we decide that your participation to that research is of relevance. The option of whether you would like or not to be recontacted for future research is entirely up to you also. Please, indicate your option by initializing below:

_____ Yes, I would like to be contacted in the future for other research.

_____ No, I do not wish to be contacted in the future for other research.

The purpose of this project is to develop new knowledge about the causes and risk factors of developing cancer in children. Because the studies we plan to do are research procedures for which the clinical relevance has not yet been proven, we will in general not be able to provide clinical information or any results from this research to you. Conclusive results of future studies can become available to the public when they will be published in peer reviewed scientific journals. Even then, you will not be identified by name in such publications. We will notify you if we think you may be at increased risk and the discovery has been validated independently by a second study.

Patient ID _____

CONTROL GROUP OPTION TO CONSENT TO BE CONTACTED ABOUT RESULTS:
Throughout the conduct of this study we may find out that you may have an increased risk of developing cancer, although you are not ill now. A second study will be done by our group or an independent second group of investigators. Only if our findings are confirmed we will notify you. Both studies must be published or accepted to be published in peer-reviewed medical journals before we send you a notice.

This does not mean that you have cancer, or that you will definitely develop cancer. It actually means that when we compare you to the general population, you may have an increased risk of developing a cancer in general.

If we obtain such information, we will offer you the option to receive this information individually. It is important for you to know that these will be research results only, and they must be confirmed in a clinical or diagnostic laboratory in order to be used for medical decisions. We will not track the control subjects to see if they develop cancer in the future.

If your research findings show an increased risk of cancer in general, and if you choose to receive this information, we will offer to make arrangements for you to speak to an oncologist, or to a cancer prevention counselor, to help you understand the meaning of the research results.

We will also give you information about clinical testing laboratories that provide confirmation of research results on a fee basis.

Please, let us know if you want to receive research results by checking the appropriate place below.

_____ Yes, I would like to be contacted in the future to learn the results of research studies that used my information if I am at increased risk.

_____ No, I do not wish to be contacted in the future to learn the results of research studies that used my information.

You can see and get a copy of your research related health information. Your research doctor may be able to provide you with part of your information while the study is in progress and the rest of your information at the end of the study.

Potential Risks and Discomforts
There are no additional risks related to obtaining a buccal cells sample.

Another risk may be that your saliva/ buccal cells sample and your answers to the questionnaire will be linked to your name. All reasonable efforts will be made to keep your name and identity strictly confidential throughout this study and the future studies that will utilize your information. The research data obtained from you will not be added to your medical record. Also, future publication of research results that will include information obtained from you will be anonymous.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

Potential Benefits
You will receive no direct benefit from your participation in this study. However, your participation may help the investigators better understand why cancer occurs in infants, children and adolescents. Based on the information obtained from this study, the investigators may find out about new causes that lead to cancer..

Alternatives
The following alternative procedures or treatments are available if you choose not to participate in this study: the only alternative to this study is to not participate..

Subject Costs and Payments
You will not be asked to pay any costs related to this research.

You will not be paid for taking part in this study.

Subject's Rights
Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

Your Health Information

We may be collecting health information that could be linked to you (protected health information). This protected health information might have your name, address, social security number or something else that identifies you attached to it. Federal law wants us to get your permission to use your protected health information for this study. Your signature on this form means that you give us permission to use your protected health information for this research study.

If you decide to take part in the study, your protected health information will not be given out except as allowed by law or as described in this form. Everyone working with your protected health information will work to keep this information private. The results of the data from the study may be

published. However, you will not be identified by name.

People who give medical care and ensure quality from the institutions where the research is being done, the sponsor(s) listed in the sections above, representatives of the sponsor, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study. Because of the need for the investigator and study staff to release information to these parties, complete privacy cannot be guaranteed.

The people listed above will be able to access your information for as long as they need to, even after the study is completed.

If you decide to stop taking part in the study or if you are removed from the study, you may decide that you no longer allow protected health information that identifies you to be used in this research study. Contact the study staff to tell them of this decision, and they will give you an address so that you can inform the investigator in writing. The investigator will honor your decision unless not being able to use your identifiable health information would affect the safety or quality of the research study.

The investigator, MEHMET FATIH OKCU, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: MEHMET FATIH OKCU at 832-822-1511 during the day.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child's name here _____

H-19264- EXPLORING POTENTIAL RISK FACTORS FOR CHILDHOOD CANCER AND HEMATOLOGICAL DISORDERS BY CASE-CONTROL STUDIES

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Legally Authorized Representative Parent or Guardian	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date

Patient ID _____

Appendix B: Texas-Oklahoma Pediatric Neuro-oncology Consortium Case-Control Questionnaire

PEDIATRIC CASE-CONTROL QUESTIONNAIRE

(For participants less than 18 years old)

Used by the:

TEXAS-OKLAHOMA PEDIATRIC NEURO-ONCOLOGY CONSORTIUM

and

TEXAS CHILDREN'S CANCER AND HEMATOLOGY CENTERS

INFORMATION ABOUT THE STUDY

PLEASE READ BEFORE STARTING

To the parent or legal guardian

Doctors do not understand the reasons why certain children develop cancer or hematological conditions and other do not. In order to attempt to find out what factors may be related to the development of these disorders, we need as much information as possible and, therefore, are requesting the following information from you. However, before you decide to participate, you should be aware of the following:

- **The study is voluntary**

  Your participation is voluntary. You have given your informed consent for participation in this research study. If there is any question you prefer not to answer, you may skip over it, but your response to every question is very important to this study.

- **The study is confidential**

  All responses will be kept completely confidential. In the analysis of this data, your child will be referred to as a number and only the doctors coordinating this study will associate this information with you or your child's name.

INSTRUCTIONS FOR COMPLETING THE SURVEY

- Please follow the instructions in each question carefully. Answer each question as they follow, unless given alternate instructions within the question.
- Please check the box next to the answer that best fits your situation.
- When filling information in the spaces provided, please write clearly.
- The term "participant" in this questionnaire refers to your child. The terms "birth mother" and "birth father" refer to the biological parents of the child. If you do not have any information on the birth parents, please provide as much of the other information as you can.

THANK YOU IN ADVANCE FOR YOUR PARTICIPATION

Office Use Only

Institution: _____ Record Number: _____ Study number: _____

Date Completed Questionnaire: _____ / _____ / _____ (MM/DD/YYYY)

Notes:

	Yes	No	Don't Know (DK)
Are you the **PARENT/LEGAL GUARDIAN** of the **PARTICIPANT**?..... *If your answer is **NO**, please stop here. Thank you for your time.*	☐	☐	☐
Was the **PARTICIPANT DIAGNOSED WITH CANCER** **before the current cancer (cases)** **or ever in the past (controls)** ? *If your answer is **YES**, please stop here. Thank you for your time.*	☐	☐	☐

Has the **PARTICIPANT EVER BEEN DIAGNOSED** with any of the following conditions?
Please **CHECK ALL** that apply.

If none of these apply, please check this box and continue to the next page. ☐

- ☐ AIDS/HIV infection
- ☐ Alagille syndrome
- ☐ Aniridia
- ☐ Aplastic anemia
- ☐ Ataxia-telangiectasia
- ☐ Beckwith-Wiedemann syndrome
- ☐ Blackfan-Diamond syndrome
- ☐ Bloom Syndrome
- ☐ Drash syndrome
- ☐ Enchondromatosis
- ☐ Familial adenomatous polyposis syndrome/ Gardner syndrome
- ☐ Familial colon cancer syndrome
- ☐ Fanconi anemia
- ☐ Glycogen storage diseases
- ☐ Hashimoto thyroiditis
- ☐ Hemihypertrophy syndrome
- ☐ Hirschprung disease
- ☐ Klinefelter syndrome
- ☐ Li-Fraumeni syndrome
- ☐ Multiple Endocrine Neoplasia (MEN) syndromes
- ☐ Myelodisplastic syndrome
- ☐ Neurofibromatoses
- ☐ Paget disease
- ☐ Perlman syndrome
- ☐ Phakomatoses
- ☐ Rothmund-Thomson syndrome
- ☐ Schwachman-Diamond syndrome
- ☐ Sickle Cell Anemia
- ☐ Trisomy 13
- ☐ Trisomy 18
- ☐ Down syndrome
- ☐ Tuberous sclerosis
- ☐ Turner syndrome
- ☐ Undescended testis corrected after age 2
- ☐ Viral hepatitis Type B or C
- ☐ von Hippel-Lindau disease
- ☐ Xeroderma pigmentosum

SECTION ONE

DEMOGRAPHIC INFORMATION

1. What is the participant's date of birth? _____ / _____ / _____
   MM DD YYYY

   Where was the participant born? _____
   (Town, City/State/Country)

2. ***FOR CASES ONLY:*** *(If you are completing this as a control subject, please skip to Question 3.)*
   When was the participant diagnosed with cancer/hematological condition? _____ / _____ / _____
   MM DD YYYY

3. What is the sex of the participant? ☐ Male ☐ Female

4. Is the participant of Spanish, Hispanic or Latino origin or descent? ☐ Yes ☐ No ☐ Don't know
   If Yes, mark which category best describes the participant:

   ☐ Mexican ☐ Chicano ☐ Tejano ☐ Puerto Rican ☐ Cuban ☐ Brazilian

   ☐ South American ☐ Central American ☐ Spanish Surname only ☐ Other Spanish Origin

   Please specify Other Spanish Origin _____

5. Please mark which best describes the participant's racial or ancestral background:

   ☐ White (Origins in the original peoples of Europe, Middle East, Australia, or North Africa)

   ☐ Black (Origins in any of the black racial groups of Africa)

   ☐ Asian (Origins in the original peoples of the Far East, Southeast Asia, or the Indian Subcontinent)

   If the participant is Asian, please select:

   ☐ East Asia (Hong Kong, China, Japan, Korea)

   ☐ Southeast Asian (Vietnam, Cambodia, Indonesia, Thailand, Singapore, Philippines, Malaysia)

   ☐ Indian subcontinent (India, Bangladesh, Pakistsan, Nepal, Burma)

   ☐ Native Hawaiian or Pacific Islander (Origins in the original peoples of Hawaii, Guam, Samoa, New Zealand or other Pacific Islands)

   ☐ American Indian, Native American

   ☐ Other, please describe _____

6. What is the participant's primary language? ☐ English ☐ Spanish ☐ Other: _____

7. What is the **PARTICIPANT'S CURRENT:**

   WEIGHT _____ LBS ☐ Don't know **HEIGHT**_____ FT _____IN ☐ Don't know

8. What is your relationship to the participant?

☐ Birth mother ☐ Adoptive mother ☐ Step-mother

☐ Birth father ☐ Adoptive father ☐ Step-father

☐ Legal guardian *(please specify)* _____

☐ Other relative *(please specify)* _____

If adopted, how old was the participant when he/she was adopted? _____ ☐ months ☐ years

9. Is anyone else helping you complete this questionnaire? ☐ Yes ☐ No
If Yes, who is helping you answer these questions?

☐ Study staff member ☐ Other parent ☐ Other relative

☐ Someone else *(please specify)* _____

10. What is your **CURRENT MARITAL STATUS**?

☐ Married/Living with Partner ☐ Divorced
☐ Widowed ☐ Never married
☐ Separated ☐ Other: _____

	Yes	No	DK
11. Does the **PARTICIPANT LIVE IN YOUR HOME**?	☐	☐	☐
12. Do you **OWN YOUR HOME**?	☐	☐	☐

13. What is your **TOTAL HOUSEHOLD INCOME** before taxes?

☐ Under $15,000 ☐ $50,001 - $100,000 ☐ Prefer not to answer
☐ $15,000 - $30,000 ☐ $100,001 - $150,000
☐ $30,001 - $50,000 ☐ Over $150,000

14. **HOW MANY PEOPLE** live in your home (including yourself)? _____

15. What **type of building** do you (the participant) live in? Choose one:

☐ Apartment / duplex / multiplex ☐ Trailer / Mobile home
☐ Condominium / townhouse ☐ Group quarters (dormitories)
☐ House / semi-detached house ☐ Other: _____

16. Which of the following best describes the area you (the participant) live(s) in?

☐ Rural farming
☐ Small town (less than 2,500 people)
☐ Large town (10,000 – 50,000 people)
☐ Suburban (suburb of a city with 50,000 – 1 million people)
☐ Rural non-farming
☐ Town (2,500 – 10,000 people)
☐ City (50,000 – 1 million people)
☐ Large metropolitan area (over 1 million people)
☐ Don't know

17. **RESIDENCE HISTORY**

We would like to know the addresses at which the participant lived to be able to study possible environmental exposures related to cancer risk. Start by listing the participant's current address. Then list the most recent FIVE residences in which the participant lived prior to the current address.

Also mark which was the residence when the participant was born. If you have more than 5 total addresses to list, please list the current address, the previous 4 before that, and list the address at birth as address #5.

	Address	Month / Year **started** living there?	Month / Year **stopped** living there?
CURRENT ☐ Birth Address	STREET: _____ CITY: _____ STATE: _____ ZIP: _____ COUNTRY: _____	_____ / _____ MM YYYY ☐ DK	
1 ☐ Birth Address	STREET: _____ CITY: _____ STATE: _____ ZIP: _____ COUNTRY: _____	_____ / _____ MM YYYY ☐ DK	_____ / _____ MM YYYY ☐ DK
2 ☐ Birth Address	STREET: _____ CITY: _____ STATE: _____ ZIP: _____ COUNTRY: _____	_____ / _____ MM YYYY ☐ DK	_____ / _____ MM YYYY ☐ DK
3 ☐ Birth Address	STREET: _____ CITY: _____ STATE: _____ ZIP: _____ COUNTRY: _____	_____ / _____ MM YYYY ☐ DK	_____ / _____ MM YYYY ☐ DK
4 ☐ Birth Address	STREET: _____ CITY: _____ STATE: _____ ZIP: _____ COUNTRY: _____	_____ / _____ MM YYYY ☐ DK	_____ / _____ MM YYYY ☐ DK
5 ☐ Birth Address	STREET: _____ CITY: _____ STATE: _____ ZIP: _____ COUNTRY: _____	_____ / _____ MM YYYY ☐ DK	_____ / _____ MM YYYY ☐ DK

18. Has the **PARTICIPANT, BIRTH MOTHER, or BIRTH FATHER** ever lived in an area that had any of the following work sites?

(Answer for each person and write in the space provided how long he/she lived in that area.)

If none of these apply to anyone, please check this box and continue to the next page. ☐

	When did he/she live in the area? (MM/YYYY)		
Type of Area	**PARTICIPANT**	**BIRTH MOTHER**	**BIRTH FATHER**
Chemical plant	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______
Waste dumping site	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______
Metal factory	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______
Other, specify:	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______
Other, specify:	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______
Other, specify:	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______
Other, specify:	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______	☐ Y ☐ N ☐ DK From ______ / ______ To ______ / ______

SECTION TWO

SOCIAL AND OCCUPATIONAL HISTORY

The following questions refer to the participant's BIRTH MOTHER.
Please try to answer them to the best of your ability.

19. Do you have knowledge about or information concerning the **BIRTH MOTHER** of the participant?

☐ Yes ☐ No *If No, please skip to Question 28 in this section.*

20. What is the **BIRTH MOTHER's** date of birth? _____ / _____ / _____ (MM/DD/YYYY)

21. Where was the **BIRTH MOTHER** born? _____
(Town, City/State/Country)

22. Is the **BIRTH MOTHER** of Spanish, Hispanic or Latino origin or descent? ☐ Yes ☐ No ☐ Don't know
If Yes, mark which category best describes her:

☐ Mexican ☐ Chicano ☐ Tejano ☐ Puerto Rican ☐ Cuban ☐ Brazilian

☐ South American ☐ Central American ☐ Spanish Surname only ☐ Other Spanish Origin

Please specify Other Spanish Origin _____

23. Please mark which best describes the **BIRTH MOTHER's** racial or ancestral background:

☐ White (Origins in the original peoples of Europe, Middle East, Australia, or North Africa)

☐ Black (Origins in any of the black racial groups of Africa)

☐ Asian (Origins in the original peoples of the Far East, Southeast Asia, or the Indian Subcontinent)

If the BIRTH MOTHER is Asian, please select:

☐ East Asia (Hong Kong, China, Japan, Korea)

☐ Southeast Asian (Vietnam, Cambodia, Indonesia, Thailand, Singapore, Philippines, Malaysia)

☐ Indian subcontinent (India, Bangladesh, Pakistsan, Nepal, Burma)

☐ Native Hawaiian or Pacific Islander (Origins in the original peoples of Hawaii, Guam, Samoa, New Zealand or other Pacific Islands)

☐ American Indian, Native American

☐ Other, please describe _____

24. What grade of school has the **BIRTH MOTHER** completed?

☐ Less than high school
☐ High school or GED
☐ Post high school training other than college (vocational, technical, etc.)
☐ Some college
☐ College
☐ Graduate or professional school

25. What is the **BIRTH MOTHER's** primary language? ☐ English ☐ Spanish ☐ Other: _____

	Yes	No	DK
26. Is the **BIRTH MOTHER** currently employed outside the home?.....	☐	☐	☐

If yes, what is her **JOB TITLE?** _____

What is the **INDUSTRY**? _____
*For example, if she is a "bank teller", write "teller" for **JOB TITLE** and "banking" for **INDUSTRY**.*

HOW LONG has she had this job? _____ (m or y)
For example, if she has worked this job for 5 years, 6 months, write "5y 6m" on the line above.

27. List the jobs that the **BIRTH MOTHER** has had in the **LAST 10 YEARS**, and how long she held each job. Start with the job immediately before the current one and go back in time. For duration, please indicate if the time worked at that job was in months (m) or years (y).

Job Title	Industry	Name of Employer	Duration (m or y)

The following questions refer to the participant's BIRTH FATHER.
Please try to answer them to the best of your ability.

28. Do you have knowledge about or information concerning the **BIRTH FATHER** of the participant?

☐ Yes ☐ No If No, please skip to Question 39 in the next section.

29. What is the **BIRTH FATHER's** date of birth? _____ / _____ / _____ (MM/DD/YYYY)

30. Where was the **BIRTH FATHER** born? _____
(Town, City/State/Country)

31. Is the **BIRTH FATHER** of Spanish, Hispanic or Latino origin or descent? ☐ Yes ☐ No ☐ Don't know
If Yes, mark which category best describes him:

☐ Mexican ☐ Chicano ☐ Tejano ☐ Puerto Rican ☐ Cuban ☐ Brazilian

☐ South American ☐ Central American ☐ Spanish Surname only ☐ Other Spanish Origin

Please specify Other Spanish Origin _____

32. Please mark which best describes the **BIRTH FATHER's** racial or ancestral background:

☐ White (Origins in the original peoples of Europe, Middle East, Australia, or North Africa)

☐ Black (Origins in any of the black racial groups of Africa)

☐ Asian (Origins in the original peoples of the Far East, Southeast Asia, or the Indian Subcontinent)

If the BIRTH FATHER is Asian, please select:

☐ East Asia (Hong Kong, China, Japan, Korea)

☐ Southeast Asian (Vietnam, Cambodia, Indonesia, Thailand, Singapore, Philippines, Malaysia)

☐ Indian subcontinent (India, Bangladesh, Pakistsan, Nepal, Burma)

☐ Native Hawaiian or Pacific Islander (Origins in the original peoples of Hawaii, Guam, Samoa, New Zealand or other Pacific Islands)

☐ American Indian, Native American

☐ Other, please describe _____

33. What grade of school has the **BIRTH FATHER** completed?

☐ Less than high school
☐ High school or GED
☐ Post high school training other than college (vocational, technical, etc.)
☐ Some college
☐ College
☐ Graduate or professional school

34. What is the **BIRTH FATHER's** primary language? ☐ English ☐ Spanish ☐ Other: _____

	Yes	No	DK
35. Is the **BIRTH FATHER** currently employed outside the home?.....	☐	☐	☐

If yes, what is his **JOB TITLE**: _____

What is the **INDUSTRY**: _____
*For example, if he is an "electrician", write "electrician" for **JOB TITLE** and "construction" for **INDUSTRY**.*

HOW LONG has he had this job? _____ (m or y)
For example, if he has worked this job for 5 years, 6 months, write "5y 6m" on the line above.

36. List the jobs that the **BIRTH FATHER** has had in the **LAST 10 YEARS**, and how long he held each job. Start with the job immediately before the current one and go back in time. For duration, please indicate if the time worked at that job was in months (m) or years (y).

Job Title	Industry	Name of Employer	Duration (m or y)

37. Does the **BIRTH FATHER** drink alcohol? ☐ Yes ☐ No ☐ DK

If no, please skip to Question 38.

If yes, what is his alcohol intake like?

At what age did he start drinking alcohol? _____ years

How long has he been drinking alcohol? _____ years

How many alcoholic drinks does he usually have in a week? _____ drinks/week

38. Has the **BIRTH FATHER** ever smoked cigarettes? ☐ Yes ☐ No ☐ DK

If no, please skip to Question 39.

If yes, what is his smoking pattern like?

At what age did he start smoking? _____ years

How long has he been smoking? _____ years

How many cigarettes does he usually smoke in a day? _____ cigarettes/day
Note: 1 pack = 20 cigarettes

Did he smoke cigarettes while the birth mother was pregnant with the participant? ☐ Yes ☐ No ☐ DK

If yes, How many cigarettes did he smoke each day during the pregnancy? _____ cigarettes/day
Note: 1 pack = 20 cigarettes

SECTION THREE

PRENATAL AND PERINATAL HISTORY

If you are not the BIRTH MOTHER, please skip to SECTION FOUR: INFANT HISTORY.

39. During the pregnancy with the participant, did you receive routine prenatal care? ☐ Yes ☐ No ☐ DK

The following questions refer to the:

- **entire year prior** to your pregnancy with the PARTICIPANT (**PRIOR**)
- **during** your pregnancy with the PARTICIPANT (**DURING**)

	PRIOR Y	PRIOR N	PRIOR DK	DURING Y	DURING N	DURING DK
40. Did you have an infection or illness?						
a. **VIRAL INFECTION** such as chicken pox, mononucleosis, Fifth disease, influenza, rubella, hepatitis B, sexually transmitted disease (herpes, HIV) or others.	☐	☐	☐	☐	☐	☐
b. **BACTERIAL INFECTION** such as Group B strep, sexually transmitted disease (chlamydia, gonorrhea, syphilis), bacterial vaginosis or others	☐	☐	☐	☐	☐	☐
c. **PARASITE** such as trichomoniasis or toxoplasmosis or others	☐	☐	☐	☐	☐	☐

If yes, specify the name of the infection(s).

PRIOR	DURING

If yes, specify the name of the infection(s).

PRIOR	DURING

If yes, specify the name of the infection(s).

PRIOR	DURING

41. Were there any medical conditions you experienced **during** this pregnancy? ☐ Yes ☐ No ☐ DK

If yes, please name the condition(s)

	PRIOR Y	N	DK	DURING Y	N	DK
42. Did you take any **prescribed medications?** Please do not list medicine/drugs that you buy off the shelf at the drug store (over-the-counter).						
a. **ANTIBIOTICS** such as amoxicillin, bactrim, erythromycin, penicillin or others.....	☐	☐	☐	☐	☐	☐
If yes, specify the name of the drug(s).						
PRIOR				**DURING**		
b. **BIRTH CONTROL PILLS** such as Demulen, Lo-ovral, Loestrin, ... Norinyl, Norplant, Ortho-Novum, Ovral, Triphasil or others	☐	☐	☐	☐	☐	☐
If yes, specify the name of the drug(s).						
PRIOR				**DURING**		
c. **ESTROGENS OR PROGESTERONES (FEMALE HORMONES)** such as Estrace, Estraderm patch, Premarin, Provera, Medroxyprogesterone or others.....	☐	☐	☐	☐	☐	☐
If yes, specify the name of the drug(s).						
PRIOR				**DURING**		
d. **TESTOSTERONES (MALE HORMONES)** such as Delatesteral, ... Testosterone, cypionate, enanthate or others	☐	☐	☐	☐	☐	☐
If yes, specify the name of the drug(s).						
PRIOR				**DURING**		
e. **THYROID MEDICINES** such as L-thyroxin, Levothyroid, Levothyroxin, Synthroid, Methimazole, Propylthiouracil(PTU), radioactive Iodine treatment or others.....	☐	☐	☐	☐	☐	☐
If yes, specify the name of the drug(s).						
PRIOR				**DURING**		
f. **OTHER MEDICINES TO REPLACE BODY HORMONES** such as prednisone, DDAVP (Desmopressin), hydrocortisone, growth hormones or others.....	☐	☐	☐	☐	☐	☐
If yes, specify the name of the drug(s).						
PRIOR				**DURING**		
g. **MEDICATION FOR DIABETES** such as Insulin, Diabinase, Glucotrol, Micronase, Orinase, Tolinase or others.....	☐	☐	☐	☐	☐	☐
If yes, specify the name of the drug(s).						
PRIOR				**DURING**		

	PRIOR Y	N	DK	DURING Y	N	DK
h. **MUSCLE RELAXANTS** such as Baclofen, Flexeril, Vallium, Chlorzoxazone (Paraflex), or others..... *If yes, specify the name of the drug(s).*	☐	☐	☐	☐	☐	☐

PRIOR	DURING

	PRIOR Y	N	DK	DURING Y	N	DK
i. **PRESCRIBED PAIN MEDICINES** such as Tylenol with Codeine (Tylenol #3), Ansaid, Disalcid, Feldene, Fiorecet or others..... *If yes, specify the name of the drug(s).*	☐	☐	☐	☐	☐	☐

PRIOR	DURING

	PRIOR Y	N	DK	DURING Y	N	DK
j. **ANTI-EPILEPTIC (SEIZURE) DRUGS** such as Dilantin, Phenobarbital, Depakene, Tegretol (Carbamazepine), Klonipen, Primidone (Mysoline), Zarantin or others..... *If yes, specify the name of the drug(s).*	☐	☐	☐	☐	☐	☐

PRIOR	DURING

	PRIOR Y	N	DK	DURING Y	N	DK
k. **DRUGS FOR HIGH BLOOD PRESSURE OR FOR YOUR HEART** such as Atenolol (Tenoretic), Captopril, Digoxin (Lanoxin), Lasix (Furosemide), Inderal, Methyl-Dopa, Dyazide (Triamterene), Procardia, Vasotec or others..... *If yes, specify the name of the drug(s).*	☐	☐	☐	☐	☐	☐

PRIOR	DURING

	PRIOR Y	N	DK	DURING Y	N	DK
l. **PRESCRIBED ANTACIDS** (for excess stomach acid or ulcers) such as Tagamet, (Cimetidine), Zantac (Ranitidine), Pepcid (Famotidine) or others..... *If yes, specify the name of the drug(s).*	☐	☐	☐	☐	☐	☐

PRIOR	DURING

	PRIOR Y	N	DK	DURING Y	N	DK
m. **CHEMOTHERAPY/IMMUNE SUPPRESSANTS** such as Cytoxan, Immuran, Prednisone, Ifosfamide, Methotrexate or others..... *If yes, specify the name of the drug(s).*	☐	☐	☐	☐	☐	☐

PRIOR	DURING

	PRIOR Y	N	DK	DURING Y	N	DK
n. **ANTIDEPRESSANTS OR OTHER PRESCRIBED DRUGS FOR DEPRESSION OR OTHER MOOD DISORDERS** such as Elavil, Prozac, Paxil, Zoloft, Navene, Ritalin or others..... *If yes, specify the name of the drug(s).*	☐	☐	☐	☐	☐	☐

PRIOR	DURING

	PRIOR Y	N	DK	DURING Y	N	DK
o. **ILLICIT DRUGS** such as cocaine, opiods, amphetamines, marijuana or others……	☐	☐	☐	☐	☐	☐

If yes, specify the name of the drug(s).

PRIOR	DURING

p. **FERTILITY DRUGS** such as Lupron, Pergonal, Metrodin, Progesterone, Serophene, Clomid, Fertinex, Humegon or others……..	☐	☐	☐	☐	☐	☐

If yes, specify the name of the drug(s).

PRIOR	DURING

q. **OTHER PRESCRIBED DRUGS**……	☐	☐	☐	☐	☐	☐

If yes, specify the name of the drug(s).

PRIOR	DURING

43. Did you take any **over-the-counter medications?**

a. **DIET PILLS** ……	☐	☐	☐	☐	☐	☐

If yes, specify the name of the drug(s).

PRIOR	DURING

b. **ALLERGY PILLS** such as Bendryl, Claritin, or others ……..	☐	☐	☐	☐	☐	☐

If yes, specify the name of the drug(s).

PRIOR	DURING

c. **HERBAL OR HOME REMEDIES** ……	☐	☐	☐	☐	☐	☐

If yes, specify the name of the drug(s).

PRIOR	DURING

d. **OTHER OVER-THE-COUNTER DRUGS**……	☐	☐	☐	☐	☐	☐

If yes, specify the name of the drug(s).

PRIOR	DURING

44. Were **YOU** or the **BIRTH FATHER** exposed to any of the following **CHEMICALS** for **AT LEAST 8 HOURS PER WEEK** for the

- **entire year prior** to your pregnancy with the participant **(PRIOR)**
- **during** your pregnancy with the participant **(DURING)**

	PRIOR Y	N	DK	DURING Y	N	DK
a. **PESTICIDES OR HERBICIDES** such as DDT, Chlordane, Atrazine or others.....	☐	☐	☐	☐	☐	☐

If yes, specify the name of the chemicals(s) and who was exposed Mother (M) or Father (F)

PRIOR	DURING

b. **CHEMICALS IN THE HOME** such as asbestos, solvents, paint thinners, paints, glues, or others.....	☐	☐	☐	☐	☐	☐

If yes, specify the name of the chemicals(s) and who was exposed Mother (M) or Father (F)

PRIOR	DURING

c. **CHEMICALS IN EVERYDAY LIFE** such as fertilizers, motor oils, gasoline, car and truck, Exhaust, diesel, dusts and fibers or others.....	☐	☐	☐	☐	☐	☐

If yes, specify the name of the chemicals(s) and who was exposed Mother (M) or Father (F)

PRIOR	DURING

d. **INDUSTRIAL CHEMICALS** such as radioactive materials, dry cleaning agents, PCBs, plastics, asbestos, dusts and fibers or others.....	☐	☐	☐	☐	☐	☐

If yes, specify the name of the chemicals(s) and who was exposed Mother (M) or Father (F)

PRIOR	DURING

45. Did you **SMOKE CIGARETTES**?.....	☐	☐	☐	☐	☐	☐
If yes, how many cigarettes did you smoke **PER DAY**? (***1 pack = 20 cigarettes)***				_____		
46. Did you **DRINK ALCOHOL**?.....	☐	☐	☐	☐	☐	☐
BEER?.....	☐	☐	☐	☐	☐	☐
If yes, how many beers did you drink **PER WEEK**?				_____		
LIQUOR?.....	☐	☐	☐	☐	☐	☐
If yes, how many drinks did you have **PER WEEK**?				_____		
WINE?.....	☐	☐	☐	☐	☐	☐
If yes, how many glasses of wine did you have **PER WEEK**?				_____		

47. Did you receive any X-rays or any form of radiation (excluding ultrasounds)
while you were pregnant with the participant? ☐ Yes ☐ No ☐ DK
If yes, how many times did you receive these X-rays: _____ times
How many weeks pregnant were you at the time(s)? a) _____ weeks pregnant
b) _____ weeks pregnant

48. Did you have an **AMNIOCENTESIS**?..... ☐ Yes ☐ No ☐ DK

49. Were there any **COMPLICATIONS DURING YOUR PREGNANCY** with the **PARTICIPANT?**
such as cervical insufficiency, excess amniotic fluid diabetes, hypertension (high blood pressure), anemia (low iron), low amniotic fluid or others ☐ Yes ☐ No ☐ DK
If yes, specify the name of the complication(s).

50. Were there any problems diagnosed in the baby before delivery? ☐ Yes ☐ No ☐ DK

*If yes, please explain and name any treatment given:*_____

_____

51. Was your pregnancy with the **PARTICIPANT** your **FIRST PREGNANCY**?..... ☐ Yes ☐ No

If no, **HOW MANY TOTAL** pregnancies have you had (**INCLUDE MISCARRIAGES**)? _____

How many of the following types of pregnancy outcomes have you had?

Number of LIVE BIRTHS _____

Number of MULTIPLE BIRTHS (twins, triplets, etc) _____

Number of STILLBIRTHS _____ (fetal death after 20th week of pregnancy)

Number of MISCARRIAGES _____ (loss of fetus before 20th week of pregnancy)

52. Did you see a **FERTILITY SPECIALIST** to become pregnant with the **PARTICIPANT**?

☐ Yes ☐ No ☐ DK

53. Did you take any medications to help you become pregnant with the participant? ☐ Yes ☐ No ☐ DK
If yes, please give the name of the drug(s) and how long you took them:

_____

54. Did you go through any procedure to help you become pregnant with the participant? ☐ Yes ☐ No ☐ DK
If yes, what type of procedure did you go through? *Check all that apply.*

- ☐ In vitro fertilization (IVF)
- ☐ Intra-cytoplasmic sperm injection (ICSI)
- ☐ Gamete intra-fallopian transfer (GIFT)
- ☐ Zygote intra-fallopian transfer (ZIFT)
- ☐ Egg recipient
- ☐ Intra-uterine/artificial insemination
- ☐ Other, please give name: _____
- ☐ Don't know the name of the procedure

55. How far into the pregnancy were you when you found out that you were pregnant? _____ weeks

56. How many weeks did you carry this pregnancy before the baby was born? _____ weeks

57. What was the baby's expected/ due date of delivery? _____ / _____ / _____ (MM/DD/YYYY)

58. How old were you when the baby was born? _____ years

59. How old was the biological father when the baby was born? _____ years

60. What **TYPE OF DELIVERY** did you have for this child? ☐ Vaginal ☐ C-Section

61. Were there any **COMPLICATIONS DURING THE BIRTH?** such as placenta previa, placenta abruption, pre-eclampsia, toxemia or other…… ☐ Yes ☐ No ☐ DK
If yes, specify the name of the complication(s).

SECTION FOUR

INFANT HISTORY

62. What was the participant's **WEIGHT AT BIRTH**? _____lbs _____ oz **OR** _____ grams

63. What was the participant's **LENGTH AT BIRTH** ? _____ in **OR** _____cm

64. Did the participant need to be cared for in an intensive care nursery? ☐ Yes ☐ No ☐ DK

If yes, for how long? _____ days

65. As an infant, did the participant require any of the following:

(*Check all that apply and write down for how long each treatment lasted)*

Treatment	Duration
❑ Feedings by tube	_____
❑ Oxygen therapy	_____
❑ Phototherapy (light treatment)	_____
❑ Respirator	_____
❑ Medicines by vein (IV medication)	_____
❑ Nutrition by vein	_____
❑ Blood pressure medicine	_____
	Number of times
❑ Plain chest and abdominal X-rays	_____
❑ Blood transfusions	_____

66. Were any types of medicines given to the participant during the first year of life? ☐ Yes ☐ No ☐ DK

(Check all that apply and fill in the brand name and the duration of use. ***Please indicate if the duration for each medication was in days (d), weeks (w), months (m), or years (y).***

	Type of medication	Name(s)	Duration (d, w, m, or y)
☐	Antibiotics		
☐	Steroids		
☐	Pain medication		
☐	Other		

67. Does the participant have any body asymmetry, that is, one arm or foot is bigger on one side of the body than on the other? ☐ Yes ☐ No ☐ DK

68. Was he/she born with any unusual physical features for example, cleft lip or low set ears? ☐ Yes ☐ No ☐ DK
If yes, please describe: _____

_____

69. Did you **BREASTFEED** the participant? …….. ☐ Yes ☐ No ☐ DK

If yes, for how many **MONTHS?** _____

While you were breastfeeding, how often was your baby fed expressed breast milk to drink?

_____ times per ☐ Day ☐ Week ☐ Month ☐ Year

☐ Never fed expressed breast milk ☐ Don't know ☐ Prefer not to answer

How old was your child when he/she **completely** stopped being fed breast milk?

_____ age in ☐ Days ☐ Weeks ☐ Months ☐ Years

☐ Currently Breastfeeding ☐ Don't know ☐ Prefer not to answer

How old was your child when he/she was first fed something other than breast milk or water? (for example: formula, juice, cow's milk, solid foods)

_____ age in ☐ Days ☐ Weeks ☐ Months ☐ Years

☐ Don't know ☐ Prefer not to answer

70. Did the participant drink **FORMULA**?…….. ☐ Yes ☐ No ☐ DK

If yes, for how many **MONTHS?** _____

How old was your child when he/she was first fed formula **on a daily basis**?

_____ age in ☐ Days ☐ Weeks ☐ Months ☐ Years

☐ Don't know ☐ Prefer not to answer

While your child received formula, was he/she fed _____ ?

☐ Formula only ☐ Formula and breast milk equally

☐ More formula than breast milk ☐ More breast milk than formula

☐ Don't know ☐ Prefer not to answer

What kind of formula was your child fed most often?

☐ Regular, cow's milk-based (SMA, Similac, Enfamil)

☐ Soy or soybean-based (Isomil, ProSobee, Nursoy)

☐ Other (rice-based, elemental)

☐ Don't know ☐ Prefer not to answer

How old was your child when he/she **completely** stopped being fed formula?

_____ age in ☐ Days ☐ Weeks ☐ Months ☐ Years

☐ Currently fed formula ☐ Don't know ☐ Prefer not to answer

How old was your child when he/she started drinking milk (i.e., not in formula or breast milk) **on a daily or almost daily basis**?

_____ age in ☐ Days ☐ Weeks ☐ Months ☐ Years

☐ Never on a daily basis ☐ Don't know ☐ Prefer not to answer

What kind of milk was your child fed most often?

☐ Cow's milk

☐ Soy or rice milk

☐ Almond or coconut milk

☐ Other, please specify the type: _____

☐ Don't know ☐ Prefer not to answer

Was this milk fortified with EPA/DHA? ☐ Yes ☐ No ☐ DK

71. How old was the participant when he/she started eating **SOLID FOOD** (e.g., rice cereal, baby food, crackers, or any non-liquid foods) on a daily or almost daily basis?

_____ age in ☐ Days ☐ Weeks ☐ Months ☐ Years

☐ Never on a daily basis ☐ Don't know ☐ Prefer not to answer

Which of these did you **first introduce** to your child?

☐ Baby cereal

☐ Other cereal and starches (like breakfast cereals, teething biscuits, crackers, breads, pasta, rice, etc.)

☐ Fruit

Please specify the type and how prepared: _____

☐ Vegetables

Please specify the type and how prepared: _____

☐ French fries

☐ Meat, chicken, combination dinners

☐ Fish or shellfish

☐ Peanut butter, other peanut foods or nuts

☐ Eggs

☐ Sweet foods (like candies, cookies, cake, etc.)

☐ Other

Please specify the type and how prepared: _____

☐ Don't know

☐ Prefer not to answer

Indicate how old your child was when he/she started eating the following foods on a daily or almost daily basis. If you don't know how old your child was when he/she started eating a food on a daily or almost daily basis, please leave them blank. If your child never ate this type of food on a daily or almost daily basis, mark the box next to "Never" for that type of food.

Baby cereal					☐ Never
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	
Other cereal and starches					☐ Never
(like breakfast cereals, teething biscuits, crackers, breads, pasta, rice, etc.)					
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	
Fruit					
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	
Vegetables					
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	
French fries					☐ Never
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	
Meat, chicken, combination dinners					☐ Never
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	
Fish or shellfish					☐ Never
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	
Peanut butter, other peanut foods or nuts					☐ Never
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	
Eggs					☐ Never
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	
Sweet foods (like candies, cookies, cake, etc.)					☐ Never
_____ age in	☐ Days	☐ Weeks	☐ Months	☐ Years	

Since your child was born, has he/she ever taken any _____ ?

		If YES: When did your baby/child start taking them? Please give his/her age in weeks, months, or years.	Is your baby/child still taking them? / If NO: When did your baby/child stop taking them?	On average, how many times per week has your baby/child taken during this time period?
Fluoride drops, for example, Tri-Vi-Flor or Poly-Vi-Flor	☐ Y ☐ N ☐ DK	_____ ☐ weeks ☐ months ☐ years	☐ Y ☐ N _____ ☐weeks ☐months ☐years	_____ times per week
Multi-vitamin drops, for example, Tri-Vit (Tri-Vi-Sol) or Poly-Vi-Sol	☐ Y ☐ N ☐ DK	_____ ☐ weeks ☐ months ☐ years	☐ Y ☐ N _____ ☐weeks ☐months ☐years	_____ times per week
Multi-vitamin chewable or gummies	☐ Y ☐ N ☐ DK	_____ ☐ weeks ☐ months ☐ years	☐ Y ☐ N _____ ☐weeks ☐months ☐years	_____ times per week
Iron drops	☐ Y ☐ N ☐ DK	_____ ☐ weeks ☐ months ☐ years	☐ Y ☐ N _____ ☐weeks ☐months ☐years	_____ times per week
Other vitamins or supplements, Specify type: _____	☐ Y ☐ N ☐ DK	_____ ☐ weeks ☐ months ☐ years	☐ Y ☐ N _____ ☐weeks ☐months ☐years	_____ times per week
Other vitamins or supplements, Specify type: _____	☐ Y ☐ N ☐ DK	_____ ☐ weeks ☐ months ☐ years	☐ Y ☐ N _____ ☐weeks ☐months ☐years	_____ times per week

72. Please enter the age at which the **PARTICIPANT** accomplished each of these **MILESTONES**. **For each situation, please specify if age was in months (m) or years (y).**

_____ Sat alone _____ Dressed self _____ Talked (3-word phrase)

_____ Crawled _____ Toilet trained _____ Talked (conversation)

_____ Walked alone _____ Rode tricycle _____ Learned to read

Present school grade level: _____ Present school grades: *(Circle average grade)* A B C D F

73. From birth till the age of one month old, did the participant ever have any of the following medical conditions? Check all that apply.

- ❑ Low blood sugar
- ❑ Macrosomia (large body size)
- ❑ Jaundice (white of eyes and skin appear yellow)
- ❑ Sepsis (severe generalized infection)
- ❑ Umbilical hernia (abdominal wall defect)
- ❑ Heart defect
- ❑ Macroglossia (large tongue)

74. Did the participant receive any **MEDICINE OR TREATMENT** during the first 3 months of life?
☐ Yes ☐ No ☐ DK

If yes, please list: _____

_____

75. From birth till now, has the participant ever had any other serious medical conditions? ☐ Yes ☐ No ☐ DK

Please describe:

_____

_____

_____

76. Has the participant been **IMMUNIZED**? ..... ☐ Yes ☐ No ☐ DK

If yes, is the participant **UP TO DATE** on his or her immunizations? ..... ☐ Yes ☐ No ☐ DK

If no, did you **REFUSE IMMUNIZATIONS**?..... ☐ Yes ☐ No ☐ DK

77. Did, or does, the **PARTICIPANT** attend a **DAYCARE FACILITY**?..... ☐ Yes ☐ No ☐ DK

If yes, at WHAT AGE did the participant attend daycare? _____ (YEARS)

For HOW LONG? _____ (MONTHS) _____ (YEARS)

Infectious Disease History

78. Has the participant ever had any of the following diseases? If yes, at what age was he/she **FIRST diagnosed** with that disease? **For each situation, please specify if age was in months (m) or years (y).**

Disease	Yes	No	Age of FIRST diagnosis (m or y)
Chickenpox			
Ear infections			
Hepatitis			
Pneumonia			
Pertussis (whooping cough)			
Tuberculosis			
Shingles			
Measles			
Mumps			
Rubella			
Other			

79. Has the participant ever had a **POSITIVE TEST FOR TB** (PPD test) ?..... ☐ Yes ☐ No ☐ DK

If yes, at what age? _____(YEARS)

Non-infectious Disease History

80. Has the participant ever been diagnosed with any of the following? If yes, at what age was he/she diagnosed with that disease? **For each situation, please specify if age was in months (m) or years (y).**

Disease	Yes	No	Age diagnosed (m or y)
Anemia If yes, what type:			
Asthma			
Diabetes If yes, what type: Need insulin injections?	 ☐	 ☐	
Attention Deficit/Hyperactivity (ADD or ADHD)			
Other behavioral / Psychological problems			

81. Does the participant have any **ALLERGIES** such as food, insect bites, respiratory allergens (pollen, hayfever, animal dander) or others…… ☐ Yes ☐ No ☐ DK
If yes, specify the name of the allergy(s).

Other Medical History

82. Has the participant ever experience any of the following? If yes, at what age?
For each situation, please specify if age was in months (m) or years (y).

	Yes	No	Age (m or y)
Chemical/poison/toxin			
Blood transfusion			
Trauma			

Dental X-rays (more than once a year)		
X-rays / CT scans (more than 3 times since birth)		

83. Has the participant ever been on **ANY MEDICATION** for more than **6 CONSECUTIVE WEEKS** in his or her life …… ☐ Yes ☐ No ☐ DK
If yes, specify the name of the medication(s) and how long the child was on medicine.

SECTION FIVE

FAMILY HISTORY

84. Please list any **MEDICAL CONDITIONS** that the **BIRTH MOTHER OR BIRTH FATHER** may have had:

Relationship	Cancer or other medical condition (please list all)	Age diagnosed	Date of death (if applicable)
BIRTH MOTHER			
BIRTH FATHER			

85. Please list **ALL CHILDREN BLOOD-RELATED TO STUDY PARTICIPANT** and any **MEDICAL CONDITIONS** (**including cancer**) that the sibling(s) may have had.
Please give if this is a Full (F) sib (share both parents) or Half (H) sib (share only mother or father); if it is a half sib, please tell us if they share the Mother (M) or Father (P).

	Name	Gender	Full (F) Half (H)	Maternal (M) Paternal (P)	Date of Birth	Cancer or other medical condition (please list all)	Age Diagnosed	Date of Death (if applicable)
1		M F	F H	M P				
2		M F	F H	M P				
3		M F	F H	M P				
4		M F	F H	M P				
5		M F	F H	M P				
6		M F	F H	M P				
7		M F	F H	M P				
8		M F	F H	M P				

86. Please list **ANY OTHER CLOSE RELATIVES** (grandparents, aunts, uncles, first cousins) **BLOOD-RELATED TO THE STUDY PARTICIPANT** and any **CANCER** they may have had.

Please tell us if the relative is a grant-parent (GP), Aunt/Uncle (A/U), or first Cousin (FC) and if they are related to the participant through the Birth Mother (M) or Birth Father (P).

	Name	Gender	Type of Relative	Maternal (M) Paternal (P)	Date of Birth	Cancer or other medical condition (please list all)	Age Diagnosed	Date of Death (if applicable)
1		M F	GP A/U FC	M P				
2		M F	GP A/U **FC**	M P				
3		M F	GP A/U FC	M P				
4		M F	GP A/U FC	M P				
5		M F	GP A/U FC	M P				
6		M F	GP A/U FC	M P				
7		M F	GP A/U FC	M P				
8		M F	GP A/U FC	M P				
9		M F	GP A/U FC	M P				
10		M F	GP A/U FC	M P				

87. Apart from cancer and hematological conditions, are there any other serious medical problems in the family? ☐ Yes ☐ No ☐ DK

If yes, please specify:

FOR CASES ONLY:

88. Are there any other factors that you think could have contributed to the patient's cancer/condition?

☐ Yes ☐ No

If yes, please specify:

SECTION SIX

PERMISSIONS AND CONTACT INFORMATION

Unless you have already consented to not provide access to some of these items, by participating in this research project you give us:

YOUR PERMISSION TO CONTACT YOU in the future regarding the information you have provided to us in this questionnaire.

YOUR PERMISSION TO CONTACT YOU in the future regarding other studies in which you might want to participate.

YOUR PERMISSION TO ACCESS YOUR CHILD'S MEDICAL RECORDS for additional information regarding the information you have provided to us in this questionnaire.

YOUR PERMISSION TO ACCESS YOUR CHILD'S BIRTH CERTIFICATE for additional information regarding the information you have provided to us in this questionnaire.

YOUR PERMISSION TO ACCESS YOUR CHILD'S NEONATAL BLOOD SPOT to provide a biological sample of potential exposures near the time of birth.

Please provide your **contact information** below.

Name:_____
(First Name) (Middle Name) (Last Name) (Maiden Name)

Address: _____

City: _____ State: _____ Zip/Postal Code: _____Country:_____

Preferred contact number: _____

Email Address: _____

In case you move, or we are unable to reach you at the numbers you have provided earlier, could you provide me with the name, and address, and phone number of **another person who does not live at the same address who would know how to reach you**?

Name: _____

Address: _____

City: _____ State: ____ Zip/Postal Code: _____Country:_____

Relationship: _____

Telephone: _____ ☐ Home ☐ Work ☐ Mobile

Telephone: _____ ☐ Home ☐ Work ☐ Mobile

Email Address: _____

THANK YOU VERY MUCH FOR TAKING TIME TO ANSWER OUR QUESTIONS

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