Inequalities by Race/Ethnicity and Socioeconomic Position in the Incidence and Survival of Childhood Acute Lymphoblastic Leukemia in the United States

by

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ABSTRACT

Background: Childhood acute lymphoblastic leukemia (ALL) is the most common childhood cancer in the United States. The incidence and survival of childhood ALL have been reported to be closely associated with race/ethnicity and socioeconomic position (SEP). However, the relationship between SEP and risk of childhood ALL is not conclusive. Racial and ethnic inequalities are known in survival after childhood ALL, yet it is unclear how these inequalities have changed over time in different race/ethnicity groups, following continued survival improvement over the last several decades.

Objectives: The primary objectives of this thesis research were to: 1) quantify the incidence of childhood ALL by SEP, age and sex within each race/ethnicity; 2) investigate the association between census tract-level SEP and risk of childhood ALL, and examine potential racial and ethnic differences in the association; 3) investigate the trends of racial and ethnic inequalities in survival after childhood ALL over time; 4) quantify the racial and ethnic inequalities in survival within specific age at diagnosis and sex subgroups.

Methods: This research was conducted using population-based cancer registries data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program in the United States. Children diagnosed with a first primary malignant ALL at age 0-19 years were included. Race/ethnicity was classified as non-Hispanic-Whites (NH-Whites), non-Hispanic-Blacks (NH-Blacks), Hispanics, Asian/Pacific Islanders (APIs), and American Indian/Alaska Natives (AIANs). Census tract-level composite SEP index was also obtained from the SEER data. Crude incidence rates of ALL by SEP, sex and age within each race/ethnicity group were calculated. Cumulative ALL mortalities were compared across different race/ethnicity groups. Incidence rate ratios and their 95% confidence intervals (CIs) associated with SEP and

race/ethnicity, adjusting for sex, age and year of diagnosis, were estimated using Poisson regression models with log population counts as the offset term. Multivariable Cox regression analyses were applied to estimate ALL mortality hazard ratios (HRs) associated with race/ethnicity, age at diagnosis and sex, adjusting for each other, within each diagnosis period (1975-83, 1984-91,1992-99, and 2000-10).

Results: The risk of childhood ALL was positively associated with SEP among NH-Whites, NH-Blacks, APIs, and AIANs, but was negatively associated among Hispanics. After adjusting for sex, age and year of diagnosis, as compared against children with the lowest SEP, the adjusted incidence rate ratios of children with the highest SEP were: 1.29 (95% CI, 1.15-1.44) for NH-Whites, 1.67 (95% CI, 1.20-2.34) for NH-Blacks, 1.57 (95% CI, 1.17-2.09) for APIs, 2.46 (95% CI, 0.98-6.19) for AIANs and 0.70 (95% CI, 0.60-0.81) for Hispanics. Racial and ethnic inequalities in ALL mortality among patients diminished in NH-Blacks, but increased in other racial/ethnic groups, as compared to NH-Whites, in particular among Hispanics. Specifically, compared to NH-Whites, the HR in NH-Blacks dropped to 1.21 (95% CI, 0.74-1.96) in 2000-10 from the largest inequality seen in 1984-91 (HR=2.09, 95% CI, 1.57-2.79); the HR in Hispanics increased, however, from 1.28 (95% CI, 0.98-1.66) in 1975-83 to 1.95 (95% CI, 1.48-2.58) in 2000-10. APIs and AIANs had HRs of 1.39 (95% CI, 0.92-2.11) and 2.31 (95% CI, 1.13-4.74), respectively, in 2000-10 with non-statistically significant increases over time.

Conclusions: Associations between SEP and risk of childhood ALL differed by race/ethnicity. Future study should confirm this finding and investigate potential underlying causes. Survival inequalities changed differently across subgroups of children with ALL. Underlying causes of the differential trends need to be examined, such that targeted interventions can be developed to reduce inequalities.

PREFACE

This thesis is an original work by Linwei Wang with supervison from Dr. Yutaka Yasui.

Chapter 3 of this thesis is accepted and will be published in the Cancer Epidemiology, Biomarker & Prevention as an article authored by Linwei Wang, Smita Bhatia, Scarlett Lin Gomez, Yutaka Yasui. Differential inequality trends over time in survival among US children with acute lymphoblastic leukemia by race/ethnicity, age at diagnosis and sex. I was involved in the conception and design of the study, and was responsible for the development of methodology, acquistiion of data, analysis and interpretation of the data, as well as drafting and revising the manuscript. Dr. Smita Bhatia and Dr. Scarlett Lin Gomez were involved in the interpretation of the data and revison of the manuscript. Dr. Yutaka Yasui was invloved in the conception and design of the study, development of methodology, interpretation of the data, and revison of the manuscript.

DEDICATION

I would like to dedicate this thesis to my beloved parents and sister.

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ALL	Acute Lymphoblastic Leukemia
SEP	Socioeconomic Position
WBC	White Blood Cell
NCI	National Cancer Institute
COG	Children's Oncology Group
CNS	Central Nervous System
AIAN	American Indian/Alaska Native
API	Asian/Pacific Islander
NH-White	Non-Hispanic-White
NH-Black	Non-Hispanic-Black
POG	Pediatric Oncology Group
CCG	Children's Cancer Group
SEER	Surveillance, Epidemiology, and End Results
IRR	Incidence Rate Ratio
CI	Confidence Interval
P	P-value
HR	Hazard Ratio

CHAPTER 1: INTRODUCTION

1.1 OVERVIEW

This thesis research focuses on investigation of inequalities in the incidence and survival of childhood acute lymphoblastic leukemia (ALL) in the United States, specifically inequalities by race/ethnicity and socioeconomic position (SEP). The term "childhood ALL" is used to refer to ALL cases diagnosed at age younger than 20 years.

The following literature review starts with an overview of childhood ALL, providing a general background regarding epidemiology, etiology, treatment and prognosis of the disease. Then literature on the relationship between SEP, race/ethnicity, and risk of childhood ALL is reviewed along with the concept and measurement of SEP to provide additional context for Chapter 2. Literature review on the relationship between race/ethnicity, SEP and survival after childhood ALL is also performed in support of Chapter 3. At the end, motivations and objectives of this research are discussed.

1.2 OVERVIEW OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

1.2.1 Incidence and Epidemiology

Acute lymphoblastic leukemia (ALL), also known as acute lymphocytic leukemia, is the most common childhood cancer in the United Sates, with an annual incidence of 3~4 cases per 100,000 children younger than 20 years old.[1] ALL accounts for over 25% of cancers diagnosed among children aged 0-14 years, and about 8% of cancers among adolescents aged 15-19 years.[2] It is also commonly referred to as "childhood leukemia", as about 75% to 80% of children with leukemia have ALL. The incidence of ALL peaks at age 1-4 years; slightly more males than

females are diagnosed with ALL.[3] Hispanic children appear to have the highest incidence and White children have a higher incidence than Black children.[1, 3]

1.2.2 Classifications and Etiology

ALL is a cancer of the lymphoid cells, originating in the bone marrow and the lymphoid organs of the body. It is a type of cancer in which the bone marrow makes too many immature lymphocytes (a type of white blood cells). The World Health Organization classifies ALL into B lymphoblastic leukemia (previously termed precursor B-cell ALL), and T lymphoblastic leukemia based on the immunophenotype.[4] The former type accounts for 80%-85% of childhood ALL.[5]

The etiology of ALL remains largely enigmatic. Composite causality has been considered for ALL, however, which includes interactions between exogenous or endogenous exposures, genetic susceptibility, as well as chance.[6] A two-hit model has also been proposed for the natural history of ALL: [7] a minimum of two oncogenic hits are needed to cause ALL (except infant ALL), with the first hit occurs in utero which forms a pre-leukemia clone, and a second postnatal hit is needed to unleash the malignant transformation. Two commonly recognized infective basis hypotheses regarding the etiology of ALL are Greave's "delayed infection" hypothesis, [8] and Kinlen's "population mixing" hypothesis.[9] The former postulates that that absence or diminution of infections early in life may cause uncontrolled immune reaction to later infections thus indirectly promote the malignancy. The latter postulates that marked influxes of people into rural areas will promote contacts between infected and susceptible individuals and increases the risk of ALL among susceptible individuals.

Besides infection, which is a strong candidate causal factor, exposure to ionizing radiation is an established but not significant cause for childhood leukemia, as evidenced by the studies of survivors of the Japanese atomic bomb.[10] In addition, inherited, predisposing genetic syndromes, such as Down's syndrome, Bloom's syndrome, Nijmegen breakage syndrome, and ataxia-telangiectasia are associated with a small fraction of leukemia cases (<5%).[11]

1.2.3 Treatment and Prognosis

Treatment of ALL usually consists of three phases, including remission induction, which aims to kill the leukemia cells in the blood and bone marrow; consolidation/intensification, which begins once the leukemia is in remission, and aims to kill any leukemia cells that remain in the body; and a maintenance phase, which aims to prevent relapse.[12] Four types of standard treatment are usually used, including chemotherapy, radiation therapy, chemotherapy with stem cell transplant, and targeted therapy.[12]

Currently, US children with ALL are usually treated according to the risk-based therapy, in order to reduce toxicity in low-risk patients and ensure intense treatment for high-risk patients to improve prognosis.[13-15] The two most important prognostic factors are age and white blood cell (WBC) count at diagnosis.[16, 17] Children aged 1 to younger than 10 years have better prognosis than older children, which is partially explained by more frequent occurrences of ALL with favorable cytogenetic features at a younger age.[18, 19] Infants tend to have the worst prognosis as approximately 80% of infants with ALL have an *MLL* gene rearrangement which is associated with poor prognosis.[20] Lower WBC count is considered as a favorable prognostic factor.[13, 17]

Based on the National Cancer Institute (NCI) risk group classification, children diagnosed at age 1 to younger than 10 years old with WBC count less than 50,000/μl are considered as having standard-risk ALL, and the remaining children will be classified as having high-risk ALL.[13]

Immunophenotype is another prognostic factor, and T-cell ALL is usually associated with worse clinical features and worse prognosis than B-cell ALL.[21] Different study groups modify the risk-based treatment scheme slightly based on the NCI risk group classification and immunophenotype. For example, the Children's Oncology Group (COG) assigns patients into one of the four initial groups: T-cell ALL; Infant ALL; NCI standard-risk B-cell ALL; and NCI high-risk B-cell ALL.[14] Studies have shown that with appropriately intensive therapy, the prognosis of children with T-cell ALL is approaching that of children with B-cell ALL.[21, 22]

Some other unfavorable prognostic factors include male sex,[23] presenting with central nervous system (CNS) involvement at diagnosis,[24] having Down syndrome,[25] and involving unfavorable cytogenetics/genomic alterations (e.g., Philadelphia chromosome, rearrangements of *MLL* gene).[26] Some of these factors have been incorporated to plan initial treatment to ALL patients.[27] Moreover, indicators quantifying early response to treatment (such as day 7 and day 14 bone marrow responses, induction failure) have also been used along with other prognostic factors to modify the intensity of post-induction therapy.[12, 28] Race/ethnicity is also a known prognostic factor and will be discussed in detail in the section 1.4.1.

In summary, treatment of ALL has improved significantly over time. The introduction of combination chemotherapy, development of risk-based treatment protocols placed at well-

designed therapeutic trials, applications of molecular biological tools in improving treatment precision, [29] have all contributed to changing ALL from a largely fatal disease before 1960s to a disease with near 90% 5-year survival probability in late 2000s.[3, 30]

1.3 SOCIOECONOMIC POSITION, RACE/ETHNICITY, AND RISK OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

1.3.1 Concept and Measurement of SEP

Socioeconomic position (SEP) is a broad concept commonly used in health research, referring to the social and economic factors that influence what positions individuals or groups hold within the structure of a society.[31, 32] The term "SEP" is used in this thesis work, rather than the other commonly used terms such as "socioeconomic status" or "social class", in line with the considerations discussed by Krieger *et al.*,[31] to reflect two key elements embedded in the concept: 1) actual resources, such as income and education; and 2) status, meaning prestige-, or rank-related characteristics.

Commonly used individual-level measures of SEP include education, income, and occupation; each measure captures a distinct aspect of SEP and may be more or less relevant to different health outcomes. Area-level SEP measures, which are usually aggregated from individual-level data, have also been frequently used in research, due to its availability in most census and administrative databases. For example, the US Bureau of the Census have defined several area-level SEP measures, including percentage of person below the poverty line, median household income, percentage of unemployment, which are aggregated at county, census tract or census block group levels.[33] Area-level measures are sometimes used as a proxy for individual-level

measures when the latter are not available, with limitations such as potential misclassifications. Moreover, area-level SEP measures can be used to examine how the context in which one lives influences health: this is an important concept in assessing SEP associations with health, and can be informative for purposes such as allocating public resources or interventions to specific areas.[34-36] Research in investigating both the individual effect and contextual effect of SEP in health using multilevel analysis has also been evolving.[37, 38]

Besides using a single indicator of SEP, sometimes, several SEP measures can be combined to construct a composite SEP index. In the United Kingdom, several composite SEP indices have been developed and frequently used in health research, including Carstairs deprivation index, [39] and Townsend deprivation index.[40] Although composite indices may not be recommended in use to explain the mechanism through which a specific SEP dimension generates health differences, [35, 41, 42] the availability of area-level summary SEP indices promote research on impact of SEP on health outcomes. Moreover, it has also been discussed that composite indices, which capture several aspects of SEP, may be particularly useful in studies when SEP serves as a confounder.[35]

In summary, SEP is a complex and multidimensional concept, which is hard to assess and operationalize. The strengths, limitations and the implications of different measures have been discussed in several key publications.[31, 34, 35, 43] There is no single best measure of SEP and the choice of SEP measures should be guided by research questions of interest. With this being said, in practice, the use of SEP measures is often driven by the availability of the data. For example, in the United States, sub-county level SEP measures are not publically available in cancer registry data due to the concerns about patient confidentiality, which may limit research in this

area. A census tract-based composite SEP index has been recently used by SEER to promote cancer surveillance research in the United States on impact of SEP on health while protecting the confidentiality of cancer registry data.[44]

1.3.2 SEP and Risk of Childhood ALL

Low SEP has been frequently associated with increased risk of a wide range of mental and physical diseases, including stress, [45] cardiovascular disease, [46] type 2 diabetes, [47] and some cancers (e.g., lung cancer [48] and cervical cancer [49]). Some diseases, however, have been reported to be more common among individuals or areas of high SEP, such as female breast cancer [49] and malignant melanoma.[50] Childhood leukemia is also one of those rare exceptions. A 1985 review by Greenberg and Shuster classified five out of six record-based studies as showing increased incidence of childhood leukemia with high SEP.[51] Nevertheless, recent reviews of literature have shown inconsistent evidence regarding relationship between SEP and risk of childhood leukemia, with the studies varying by calendar time, study design, the type, level and measurement point (e.g., at birth or at diagnosis) of the SEP measures, population, as well as leukemia subtypes.[41, 42]

For example, some individual-level SEP measures, such as family income, mother's education, and father's education have been predominantly reported to be negatively associated with the risk of childhood leukemia, while father's occupational class has been mostly reported to be positively associated with risk of childhood leukemia.[41] It is possible that different SEP measures, which capture different aspects of SEP, have different associations with risk of diseases. However, father's occupational class has been mostly studied in European countries and in record-based studies, while the other measures have been studied in North America in

case-control studies, which involve an interview or questionnaire component. Therefore, the observed inconsistent results can also be due to study design and/or the population. In record-based studies, cases of low SEP may be under-diagnosed, or under-recorded, which may bias the results toward the positive association. In contrast, in case-control studies, selection bias has been discussed to be a large concern and over-representation of controls of high SEP may bias the results toward the negative association.[52]

Studies examining area-level SEP measures and risk of childhood leukemia have also presented inconsistent results. Record-based studies from UK consistently reported a positive association between census ward-level SEP measures and risk of childhood leukemia in both earlier (1970s) and recent (2000s) periods.[53-55] A Canadian population-based study also reported a positive association.[56] In contrast, a large population-based case-control study in UK reported no association between census ward-level deprivation score measured either at time of diagnosis or at birth and risk of childhood leukemia.[57] Another recent population-based case-control study in Switzerland also found no association.[58] In the United States, most studies were conducted in earlier periods (included cases earlier than 1994), and census tract-level income, home conditions and rental cost, were found to be positively associated with risk of childhood leukemia.[41] Recent studies on area-level SEP measures and risk of childhood leukemia are limited in the US. Two studies used county-level SEP measures: one reported increased risk of ALL in females but not in males in more affluent counties;[59] and the other reported elevated risk of leukemia in Blacks, but decreased risk for Whites, in more affluent counties.[60]

In summary, more studies on association between SEP and risk of childhood ALL have been suggested and considerations should be given to distinguish different SEP measures, minimize bias, and provide necessary comparisons with previous studies to separately examine the effect of study design, population characteristics, SEP measures and calendar time on the direction of the results.[41, 42]

1.3.3 Race/Ethnicity and Risk of Childhood ALL

The US population is racially and ethnically diverse. The federal government has recognized five minimum categories for race, including American Indian/Alaska Native (AIAN), Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White; and two categories for ethnicity, including "Hispanic or Latino" and "Not Hispanic or Latino".[61] According to US federal classifications, race and ethnicity are two different concepts. The term "non-Hispanic" can be used to refer to all people of any race whose ethnicity is not Hispanic or Latino. In 2013, about 77.7% population identified themselves as White, and around 13.2%, 1.2%, 5.3%, 0.2%, and 17.1% of population self-identified as Black or African American, AIAN, Asian, Native Hawaiian or Other Pacific Islander, and Hispanic or Latino, respectively.[62] In this thesis research, the term "race/ethnicity" is used to refer to discussions involving either race or ethnicity or both.

Racial and ethnical differences in incidence of childhood ALL have been reported. Hispanic children have the highest risk of childhood ALL, with an annual incidence rate over 40 per million.[63, 64] White children have a substantially higher incidence than Black children, with

annual incidence rates of around 36 per million and 15 per million, respectively.[64, 65] Asian and Pacific Islander (API) children have been reported to have similar incidence as White children.[64]

Part of the racial and ethnic inequalities in incidence can be explained by genetic differences. Several genomic loci have been found to be associated with susceptibility of ALL and the risk alleles distribute unequally across racial and ethnic groups.[66] For example, several genome-wide association studies reported germline variants in *ARID5B* gene to be strongly associated with ALL susceptibility, with some variants specific to Whites and Hispanics, and some risk alleles being more common among Hispanics and Whites, and substantially less common in Blacks. [67, 68] In addition, the *PIP4K2A* gene has been suggested to be associated with risk of ALL, with risk allele frequency paralleling racial and ethnic differences in the incidence of ALL.[69] Nevertheless, a large proportion of difference in risk of childhood ALL by race/ethnicity remains unexplained.

1.3.4 Differential SEP-ALL-Risk Associations by Race/Ethnicity

The relationship between SEP and risk of childhood ALL, as well as relationship between race/ethnicity and risk of childhood ALL have been individually studied as summarized above. Research is limited, however, in examining potential racial and ethnic differences in the SEP-ALL-risk association. The SEP measures may have different relative meanings within each racial and ethnic group, and race/ethnicity related cultural and biological factors may modify the influence of SEP. Therefore, the effect of SEP on cancer risks may differ by race/ethnicity. Such differences have been found in adult cancers. Breast cancer incidence was reported to increase with affluence only among Hispanic women, and lung cancer incidence was reported to increase with socioeconomic deprivation among non-Hispanic-Whites (NH-Whites), non-Hispanic Blacks

(NH-Blacks), and APIs, but decrease among Hispanics in the United States.[49] Moreover, racial and ethnic differences in relationship between SEP and risk of childhood ALL have also been suggested. One ecological study reported elevated risk of leukemia in Blacks, but decreased risk for Whites in more affluent counties in the United States, as discussed in section 1.3.2.[60] Therefore, future research should consider potential racial and ethnic differences in the association between SEP and risk of childhood ALL.

1.4 SOCIOECONOMIC POSITION, RACE/ETHNICITY, AND SURVIVAL AFTER CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

1.4.1 Racial and Ethnic Inequalities in Survival

Survival of ALL has improved dramatically over time. However, not all racial and ethnic groups benefit equally.[70] Racial and ethnic inequalities in survival after childhood ALL have been reported by many studies, including population-based studies using data from the SEER program, [65, 71-73] studies from single institutions, [74, 75] and studies from cooperative groups.[76-78]

Inequality in survival between Blacks and Whites has been investigated the most. Studies have consistently shown that Black children have a worse survival than White children.[71-73, 76, 77] Hispanics have also been reported to have worse survival than non-Hispanics or NH-Whites.[71-73, 76, 77] Fewer studies have been done on other racial minorities such as APIs and AIANs, which may be due to the small proportion of these minority groups in the US. APIs have been reported to have a similar or better outcome than Whites.[71, 77] AIANs have worse survival than NH-Whites.[71, 73] According to a population-based study using data from nine cancer registries in the SEER program, the five year survival probabilities were 84% for NH-Whites, and 75% for NH-

Blacks, 72% for Hispanics, 81% for APIs, and 72% for AIANs in 1990-1999.[71] Worse prognosis among Blacks and Hispanics as compared to Whites was also observed in studies of children treated at cooperative group trials who received contemporary risk-based therapy from 1980s through 1990s.[76, 77]

Different spectrum of ALL subtypes and variations in clinical presentation and tumor biology may explain at least partially the racial/ethnic survival differences. Compared to Whites, Blacks have been reported to have a higher frequency of T-cell ALL, a lower frequency of B-cell ALL (the subtype with favorable prognosis), and present with higher WBC count and CNS involvement at diagnosis, all of which reflect an increased risk of poor prognosis.[76] However, for children treated at St Jude Children's Research Hospital, where patients were treated with contemporary multimodality therapy according to therapeutic protocols regardless of race/ethnicity, or ability or pay for their medical care, no difference was found in survival of Blacks as compared to Whites in treatment eras from 1984 through 2007.[74, 75] This supports the hypothesis that, with equal access to contemporary, risk-based treatment, there is likely no Black-White inequality in ALL mortality.

Variations in adherence to treatment may also explain some racial and ethnic differences, as adherence to treatment is important in the maintenance phase of ALL treatment to prevent relapse. Blacks and Hispanics have been reported to have a lower adherence rate than NH-Whites, which is associated with increased risk of relapse.[79] However, one study showed that with an adherence rate of 90% or more, Hispanics continued to demonstrate increased rates of relapse.[79, 80] Moreover, after adjusting for the above mentioned clinical factors, as well as

measures of adherence to treatment, a Pediatric Oncology Group (POG) Study still found significantly worse survival among Blacks and Hispanics than Whites, [76] and a Children's Cancer Group Study (CCG) found inclusion of information on certain socioeconomic indices in addition to the clinical factors did not explain the worse outcomes among Blacks than Whites, but explained to some extent the worse outcomes among Hispanics as compared to Whites.[77] Both studies suggested that other factors such as variations in chemotherapeutic response to therapy may be responsible for the racial and ethnic differences.

Recent investigations have also shown certain genomic variations which may also explain partly the differences. For example, genomic rearrangement of *cytokine receptor-like factor 2* was found to be associated with poor outcome in pediatric B-progenitor ALL and was more common among Hispanics.[81] Native American ancestry has been found to be significantly associated with risk of ALL relapse due to genetic variation, [82] explaining partly the racial difference. However, clinical trials have suggested that the increased risk of relapse associated with Native American ancestry can be possibly overcome by individualized chemotherapy.[66]

In addition, the heterogeneity of Hispanic population (e.g., Mexican, Puerto Rican, and Cuban) also complicates the interpretation of the ethnic difference. A population-based study reported variations in the ethnic differences in survival after childhood ALL: compared to NH-Whites, the hazard ratio of all-cause mortality among cases varied from 1.86 for Mexicans to 4.06 for Puerto Rican, [73] suggesting potentially different reasons underlying the inequality in survival across Hispanic subgroups. Variations in survival among API subgroups have also been reported, with

Vietnamese and Filipinos faring significantly worse than non-Hispanic Whites, while Chinese, Pacific Islanders, and South Asians having similar survival, as compared to NH-Whites.[73]

1.4.2 Socioeconomic Inequalities in Survival

Socioeconomic inequalities in survival among adult cancers have been well documented universally, [83, 84] with low SEP associated with poor survival, regardless of the SEP measures used. Stage at diagnosis and differences in treatment have been cited as the most important explanatory factors of the inequality, and the greatest differences have been observed among breast cancer, bladder cancer, colorectal cancer, and cervical cancer, which have relatively good prognosis.[83, 84]

Socioeconomic inequalities in survival have also been reported in childhood ALL, with extensive evidence from less-developed countries, suggesting worse prognosis among children of low SEP.[85-89] However, evidence is less convincing in developed countries, [90-99] and socioeconomic inequalities in survival, if exist, the magnitude may be small in developed countries.[94, 97, 99] Earlier studies in Australia [90] and Greece [91] associated upper social class and car ownership with better survival; recent studies in Australia [95] and Ireland [96] showed only a weak trend of association between greater area-level deprivation and worse outcomes. There was little evidence in association of survival after childhood ALL, with parental education level in the Netherlands,[92] individual-level family income and parental education in the West Germany,[98] and area-level deprivation in the UK.[94] However, another relatively recent UK study found significant socioeconomic inequalities in ALL survival when area-based deprivation scores or father's occupational social class at the time of the child's birth were used as markers of SEP.[98]

US patients residing in lower SEP neighborhoods (measured by a composite SEP index at the census block group-level) were also found to have increased risk of death after childhood ALL as compared to those living in higher SEP areas, after adjusting for known prognostic factors including race/ethnicity.[99]

The rapid progression of childhood ALL, and the maintenance phase of ALL treatment, may present challenges in accessing to and maintaining of quality care, especially among under-resourced ALL patients. Regional differences in survival have been observed among British patients, with the most pronounced differences in the first six months after diagnosis, suggesting differential access to centralized pediatric oncology services or treatment protocols to be associated with differential childhood ALL outcomes.[93] In the United States, Blacks and Hispanics, who generally have lower SEP, have been found to be under-represented in therapeutic trials, which provide the most advanced treatment protocols.[100] However, evidence is limited in directly associating SEP with access to treatment for childhood ALL. Non-adherence to treatment has been commonly suggested to explain at least partly the socioeconomic inequalities.[85, 97, 101] A UK study found socioeconomic inequalities in survival became more striking when treatment management moved from hospital to home, suggesting adherence to treatment in the maintenance phase other than treatment accessibility to be responsible for the observed socioeconomic inequalities.[97] Nevertheless, direct association between SEP and treatment adherence among children with ALL also awaits future evidence. In addition, malnourishment has been suggested to explain partly the socioeconomic inequalities in ALL survival in developing countries.[86, 102]

1.4.3 Differential Socioeconomic Inequalities in Survival by Race/Ethnicity

Race/ethnicity and SEP are highly correlated factors. For example, in the United States, parents of Hispanic and Black children are less likely than White counterparts to have annual household income exceeding $30,000 and are more likely to have received less than high school education; [77] Black children with ALL are more likely to have public insurance and less likely to have private insurance than White children.[103] Race/ethnicity and SEP are closely linked with each other in influencing cancer survival.[94, 99, 104, 105] One common practice is to estimate the effect of one while adjusting for the other, assuming the same racial and ethnic inequalities across different SEP levels, as well as the same relative meaning of SEP across different racial and ethnic groups. A recent population-based cohort study on childhood ALL cases in California reported persistent racial and ethnic inequalities as well as socioeconomic inequalities in survival after adjusting for each other,[99] suggesting that both SEP and race/ethnicity also independently associated with health outcomes.

Another common practice is to examine the effect modification by race/ethnicity on the SEP-ALL-survival association, as SEP measures may have different relative meanings within each racial and ethnic group, resulting in differences in influence of SEP. There are two commonly used hypotheses in explaining the differential SEP-ALL-survival associations by race/ethnicity.[106] One is the minority poverty hypothesis, which centers on the belief that only racial/ethnic minorities with low SEP will experience unique disadvantages in health and health care. The other is the diminishing returns hypothesis, which centers on the belief that only Whites with high SEP will experience unique advantages in health and health care. Statistically significant differences across race/ethnicity groups were observed in socioeconomic inequalities

in survival of colorectal and female breast cancers.[105] Shorter survival was also found to be significantly associated with lower neighborhood SEP only for NH-Whites, but not for other racial and ethnic groups, among children, adolescents and young adults with leukemia in California.[94] Inclusion of SEP in the multivariable model was reported to mitigate the racial and ethnic inequalities in ALL survival as compared to Whites only for Hispanics and Asians, but not for Blacks.[77] These findings all suggest the need to examine the joint effect of race/ethnicity and SEP on survival after childhood ALL, especially when sample size is sufficient to allow analysis with enough power.

1.5 MOTIVATIONS AND OBJECTIVES

1.5.1 Research Motivations

Health inequalities research or health disparities research is burgeoning globally in the past several decades, following several health policy initiatives. In the United States, the Department of Health and Human Services included "reduce health disparities" as one of the overarching goals in its *Healthy People 2000* in 1990, which was strengthened in *Healthy People 2010* as "eliminate health disparities", and was expanded to "achieve health equity, eliminate disparities, and improve the health of all groups" in *Healthy People 2020*.[107] The National Institute of Health of the United States defines health disparities research to include basic, clinical and social sciences studies that focus on identifying, understanding, preventing, diagnosing, and treating health conditions such as diseases, disorders, and other conditions that are unique to, more serious, or more prevalent in subpopulations.[108] Research has been focused on quantifying, understanding, improving the health inequalities, and monitoring the trend of the inequalities over time.

Health disparities experienced by children are of special importance as disparities during childhood can result in a wide variety of health disparities in adulthood, influencing the health across the life course.[109, 110] Research on health disparities among children is crucial and the American Academy of Pediatrics recommends that research on eliminating health and health care disparities related to race/ethnicity and SEP to be a priority.[109]

Numerous studies have been conducted in investigating the racial/ethnic and socioeconomic differences in the incidence and survival of childhood ALL as summarized above. Several gaps in research, however, have been identified in the context of the United States. First, existing evidence on association between SEP and risk of childhood ALL is inconsistent across different calendar time periods, study designs and SEP measures. In the United States, record-based studies to examine socioeconomic differences in risk of childhood ALL in recent periods are limited. Such studies have been suggested so that results can be compared to previous record-based studies, or recent case-control studies, to separately examine the effect of calendar time and study design on the results.[41, 42] In addition, differences have been observed between Blacks and Whites in the direction of the association between county-level SEP and risk of childhood leukemia in one study,[60] but such difference has never been investigated by other studies, and potential differences across other racial and ethnic groups have never been reported. In Chapter 2 of my thesis, I investigate the association between census tract-level SEP and risk of childhood ALL in the period of 2000-2010, using population-based data, based on a hypothesis that the SEP-ALL-risk association varies by race/ethnicity. Moreover, results will be discussed in relation to the infection-based hypotheses regarding the etiology of ALL.

Second, racial and ethnic inequalities in survival after ALL among US children have been identified for a long time. Possible reasons for the inequalities have been investigated and some prognostic factors have been incorporated into the contemporary treatment protocols to address worse prognosis suffered by certain groups. The overall five-year survival probability has been reported to reach 90% in late 2000s.[3] Several studies have suggested diminishing inequality between Blacks and Whites in survival among children with ALL.[65, 78] However, the trends of the inequalities over time have not yet been quantified for other racial and ethnic groups. Studies in analyzing disparity trends are also lacking for health disparities research in general, and research to monitor the health disparity trends has been suggested.[111] In addition, studies have been limited in describing inequalities among minority groups such as APIs and AIANs, especially in recent diagnosis periods. Moreover, racial and ethnic inequalities in survival among children of certain age and sex subgroups have not been quantified. In this thesis research, I address these gaps by investigating the inequalities in survival after ALL among US children by race/ethnicity, age at diagnosis, and sex over the period of 1975-2010.

1.5.2 Research Objectives

The primary objectives of this thesis research, using population-based cancer registry data from the NCI, Surveillance, Epidemiology, End Results (SEER) program in the United States, are to:

1. Describe the incidence of childhood ALL in the United States in the period of 2000-2010
    1.1. Quantify the incidence of childhood ALL by SEP, age and sex within different racial and ethnic groups

1.2. Examine association between census tract-level SEP and risk of childhood ALL, and potential racial and ethnic differences in the association

1.3. Discuss the hypotheses regarding the etiology of childhood ALL in relation to incidence variations in 1.1 and 1.2

2. Describe inequalities in survival after ALL among US children by race/ethnicity, age at diagnosis, and sex, over the period of 1975-2010

2.1. Investigate the trends of racial and ethnic inequalities over time

2.2. Quantify racial and ethnic inequalities in survival within specific age at diagnosis and sex subgroups

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CHAPTER 2: RACIAL AND ETHNIC DIFFERENCES IN SOCIOECONOMIC POSITION AND RISK OF CHILHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

2.1 INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer in the United States, with an annual incidence of 3~4 cases per 100,000 children aged younger than 20 years.[1] Although the treatment improvement has changed childhood ALL from a highly fatal cancer before 1960s to a disease with about 90% five-year survival probability in late 2000s, [2, 3] the disease etiology remains largely enigmatic. Moreover, an increase in the incidence of childhood ALL has been reported in the United States.[3]

Affluent countries usually have higher incidence of childhood ALL than less affluent countries.[4-6] Several record-based studies in 1980s have suggested a positive association between socioeconomic position (SEP) and risk of childhood ALL.[7] These have led to speculations about several potential etiological factors for childhood ALL related to affluent life styles.

There are two commonly recognized hypotheses for the etiology of ALL. One is Greave's "delayed infection" hypothesis, which postulates that absence or diminution of infections early in life will cause uncontrolled immune responses to later infections and indirectly promote the malignancy.[8] Another is Kinlen's "population mixing" hypothesis, which indicates that certain infectious agent(s) are responsible for the disease, although no agent has been confirmed. It postulates that marked influxes of people into rural areas, where there is a higher proportion of the population that would not have been exposed to the certain infectious agent before, will promote contacts between infected and susceptible individuals and therefore increases risk of

ALL among susceptible individuals.[9] Both hypotheses are consistent with the positive association found between SEP and risk of childhood ALL.

Several more recent studies reported a negative association, [10] however, raising a question about whether there has been a change in the relationship between SEP and risk of ALL over time. As the more recent studies were all case-control studies involving interviews or questionnaires, the negative association might also be due to control selection bias and/or recall bias.[10] A UK record-based study examined the association longitudinally over three decades and found persistent evidence of higher incidence in more affluent communities.[11] Record-based studies on association between SEP and risk of ALL in recent periods among US children are needed. Moreover, poor counties in the United States were reported to have higher incidence rates of leukemia than affluent counties among whites, but lower rates among blacks, [12] indicating potential racial differences regarding the relationship between SEP and risk of leukemia.

The current study investigates the relationship between census tract-level SEP and incidence of childhood ALL using population-based cancer registry data in the United States in the period of 2000-2010. Differences in the relationship between SEP and risk of ALL among non-Hispanic Whites (NH-Whites), non-Hispanic Blacks (NH-Blacks), Hispanics, Asian/Pacific Islanders (API) and American Indian/Alaska Natives (AIANs) were evaluated. In addition, potential etiological hypotheses were discussed in explaining the observed associations between SEP and risk of ALL.

2.2 METHODS

2.2.1 Study Population

First primary malignant ALL cases among children aged 0 to 19 years diagnosed during 2000-2010 were ascertained based on the Surveillance, Epidemiology and End Results (SEER) program of the US National Cancer Institute (NCI). From 2000 onward, the SEER program expanded its data collection through population-based cancer registries to 18 selected states or metropolitan areas (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Greater California, Kentucky, Louisiana, New Jersey, Greater Georgia and the Alaska Native Tumor Registry), covering approximately 28% of the US population.[13] This study restricted the population and cases to 16 cancer registries and their areas: the Alaska Native Tumor Registry and Louisiana Registry were excluded as the census tract-level SEP information was unavailable from these two registries.[14] ALL cases were ascertained according to the International Classification of Diseases for Oncology, Third Edition.[15]

The population counts data by single-calendar year, sex, age, race, Hispanic origin, and census tract were obtained from the NCI SEER custom population database,which were based on Woods & Poole census tract estimates linked to the SEER 18 Census 2000 Geographies.[16]

2.2.2 Socio-demographics

Race and Hispanic ethnicity data in SEER registries are generally derived from information abstracted from patients' medical records and is mainly based on self- or caregiver-report, but may be based on medical staff observation.[17] Hispanic identification was additionally enhanced

using the North American Association for Central Cancer Registries Hispanic-Latino identification algorithm,[18] which was based on surnames and birthplace. Mutually-exclusive racial and ethnic categories were defined as Hispanics, NH-Whites, NH-Blacks, APIs, and AIANs. Age at diagnosis was categorized into five categories (<1 years, 1-4 years, 5-9 years, 10-14 years and 15-19 years).

SEP was assessed using a census tract-level composite SEP index developed by SEER [14] using principal components analysis on SEP measures identified by Yost *et al.*.[19] The SEP index captured seven aspects of SEP, including proportion of working class; proportion of persons aged over 16 years who are unemployed; proportion of persons below 150% of poverty line; median household income; education index (weighted school years); median house value; and median rent of a residence. Census tracts in the United States have an average population of approximately 4,000, which are designed to be relatively homogeneous units with respect to population characteristics, economic status, and living conditions.[20] Cases were mapped to their year 2000 census tract of residence based on their address at the time of diagnosis. An SEP index was assigned to each census tract and was categorized into quintiles across the SEER regions. An 'unknown' category of SEP was assigned to census tracts with missing information on one or more measures (0.68% of the census tracts have missing SEP information).[14]

2.2.3 Statistical Analyses

Crude incidence rates (IRs) of ALL by SEP, sex and age within each race/ethnicity group were calculated. Incidence rate ratios (IRRs) and their 95% confidence intervals (CIs) comparing each SEP quintile to the lowest SEP quintile within each race/ethnicity group, adjusting for sex, age

and year of diagnosis, were estimated using multivariable Poisson regression models with the log population counts as the offset term. Tests of a linear trend in the SEP effect were performed by treating the SEP variable as continous in the Poisson regression models.The association between SEP and incidence of childhood ALL within each race/ethnicity was further investigated through stratified analyses by age at diagnosis and by sex. Two-sided P-values (P) were reported and those less than 0.05 were considered statistically significant. SAS, version 9.4 was used for all statistical analyses and R, version 2.13.1 was used for producing graphs.

2.3 RESULTS

A total of 8377 children were diagnosed with ALL during 2000-2010 in the 16 registries of the SEER program. Among them, there were 46.7% NH-Whites, 38.9% Hispanics, 7.5% APIs, 6.2% NH-Blacks and 0.8% AIANs. More boys (57.1%) than girls (42.9%) were diagnosed with ALL. Children aged 1-4 years comprised the largest proportion of ALL cases (44.3%), followed by children aged 5-9 years (24.3%), 10-14 years (15.7%), 15-19 years (12.8) and infants (2.9%).

Crude incidence rates of ALL among all children, and among children in each race/ethnicity group are shown in **Table 2-1,** stratified by sex, age and SEP. Overall, about 3~4 US children per 100,000 population were diagnosed with ALL before age 20 years. Among them, Hispanics had the highest incidence rate (IR=4.54, 95% CI, 4.39-4.70, per 100, 000) and NH-Blacks had the lowest (IR=1.70, 95% CI, 1.56-1.85, per 100, 000). NH-Whites, APIs and AIANs had similar incidence rates of about 3 cases per 100,000 population. Boys were more likely to have ALL than girls regardless of their race/ethnicity. The same age peak of ALL incidence, age 1-4 years, was observed for children of any race/ethnicity, with over 8 cases per 100,000 population among

NH-Whites and Hispanics, around 7 cases per 100, 000 population among APIs and AIANs, and about 3 cases per 100, 000 NH-Blacks. Except for infants, the ALL incidence rates consistently reduced with the increase of age, but with different magnitudes, across race/ethnicity groups.

For all children combined, there appeared to be no difference in the crude (unadjusted) incidence rates of ALL across SEP quintiles. However, within each race/ethnicity group of NH-Whites, NH-Blacks, APIs and AIANs, children of higher SEP appeared to have higher incidence of ALL as compared to those of lower SEP. Comparing children with the lowest SEP to the highest SEP, the incidence rate increased from 2.81 cases to 3.60 cases, from 1.42 cases to 2.24 cases, from 2.24 cases to 3.65 cases, and from 2.07 cases to 4.88 cases per 100,000 among NH-Whites, NH-Blacks, APIs and AIANs, respectively. However, Hispanics of higher SEP had lower incidence of ALL than Hispanics of lower SEP: the crude incidence rate reduced from 4.94 cases to 3.29 cases per 100,000 among Hispanics, comparing the lowest SEP to the highest SEP.

After adjusting for sex, age and year of diagnosis, race/ethnicity-specific incidence rate ratios of childhood ALL associated with SEP are shown in **Table 2-2**. The positive association between SEP and incidence rate of ALL among NH-Blacks ($P<0.001$), NH-Whites ($P<0.004$), APIs ($P<0.001$), and AIANs ($P=0.085$), and the negative association ($P<0.001$) in Hispanics, remained after the adjustments. As compared against children with the lowest SEP, the adjusted incidence rate ratios for children with the highest SEP of the same race/ethnicity were: 1.29 (95% CI, 1.15-1.44) for NH-Whites, 1.67 (95% CI, 1.20-2.34) for NH-Blacks, 1.57 (95% CI, 1.17-2.09) for APIs, 2.46 (95% CI, 0.98-6.19) for AIANs and 0.70 (95% CI, 0.60-0.81) for Hispanics.

Figure 2-1 and Supplementary Table 2-1 show the crude incidence rates of childhood ALL by SEP and race/ethnicity, stratified by age, and by sex. It appeared infants with medium SEP had the lowest incidence rate of ALL, as compared to infants of other SEP quintiles, regardless of their race/ethnicity. The association between SEP and incidence rate of ALL within each race/ethnicity group seemed to vary by age but mostly consistent between boys and girls, except for AIANs. The incidence rates of ALL appeared to vary less by SEP among NH-Whites and NH-Blacks in older age groups.

After adjusting for sex and year of diagnosis, race/ethnicity and age-specific incidence rate ratios of childhood ALL associated with SEP are shown in **Table 2-3**. The negative association between SEP and incidence rate of ALL was observed among Hispanics diagnosed at any age group except for infants; moreover the magnitude of such association increased with the increase of age; comparing Hispanics with the highest SEP to the lowest SEP, the adjusted IRRs were 0.81 (95% CI, 0.69-0.96), 0.64 (95% CI, 0.53-0.77), 0.59 (95% CI, 0.47-0.72) and 0.56 (95% CI, 0.44-0.71) for age 1-4 years, 5-9 years, 10-14 years, and 15-19 years, respectively. For NH-Blacks, the positive association between SEP and incidence rate of ALL was statistically significant among age 1-4 years (IRRs=2.00, 95% CI, 1.41-2.82, trend-P<0.001, comparing the highest to lowest SEP) and among age 5-9 years (IRRs=1.56, 95% CI, 1.09-2.23, trend-P=0.004, comparing the highest to lowest SES), but marginally significant among age 10-14 and 15-19 years. For NH-Whites, statistically significant positive associations between SEP and risk of ALL were seen among children aged 1-4 years (trend-P<0.001) and 5-9 years (trend-P=0.017), but not among children aged 10-14 years or 15-19 years. Comparing NH-Whites with the highest SEP to those with the lowest SEP, the adjusted IRRs were 1.53 (95% CI, 1.34-1.76), 1.20 (95%

CI, 1.02-1.41), 1.10 (95% CI, 0.91-1.33) and 1.05 (95% CI, 0.86-1.30) for age 1-4 years, 5-9 years, 10-14 years, and 15-19 years, respectively. For APIs, the positive associations were statistically significant among those aged1-4 years (trend-P<0.001) and 5-9 years (trend-P=0.003), and marginally significant among those aged 10-14 years (trend-P=0.087), with the IRRs of 1.85 (95% CI, 1.38-2.50), 1.45 (95% CI, 1.07-1.98), and 1.33 (95% CI, 0.96-1.85) respectively, comparing the highest SEP to the lowest SEP. A positive association between SEP and risk of ALL was also observed among AIANs diagnosed at age 1-4 years (IRR=2.94, 95% CI, 1.16-7.42, trend-P=0.028).

2.4 DISCUSSION

The current study is to our knowledge the first study to report ethnic difference in the relationship between SEP and risk of childhood ALL in the United States. We found negative association between SEP and risk of childhood ALL among Hispanics, after adjusting for age, sex and year of diagnosis, in contrast to the positive association observed among NH-Whites, NH-Blacks, APIs and AIANs.

The distinct pattern of relationship between SEP and risk of childhood ALL among US Hispanics is a new observation; however, it agrees with several facts/evidence from previous studies. First, risk of childhood ALL varies significantly by countries, with higher incidence among developed countries.[4] However, the incidence of childhood ALL in Mexico is among the highest in the world, [5, 6] regardless of its relatively low SEP level. Second, Maria *et al.* reported a negative correlation between the municipal human development indices (a composite statistics of life expectancy, education, and per capita income, which was used to measure human

development) of boroughs of Mexico City and incidence of ALL, and a positive correlation between the average number of persons per household and the incidence of ALL, [6] which are consistent with the negative association among Hispanics in the current study. Third, ethnic difference has also been reported in the relationship between daycare attendance and risk of childhood ALL. Daycare attendance, one of the most commonly used proxies for early immune stimulation, has been consistently suggested to be protective against developing childhood ALL,[21] providing evidence supporting the delayed infection hypothesis.[8] However, one study using data from the Northern California Childhood Leukemia Study reported protective effect of daycare attendance among NH-Whites, but no association was observed for Hispanics,[22] indicating lack of evidence for delayed infection hypothesis for ALL cases diagnosed among Hispanics.

The positive associations between SEP and risk of childhood ALL observed among the four race groups are consistent with several previous studies. A Canadian population-based study associated high neighborhood income with higher incidence of childhood leukemia.[23] Another record-based study from the UK reported higher incidence among census wards with lower deprivation index.[24] The magnitude of the association is small in both studies, as well as in the current study for NH-Whites. However, two large population-based case-control studies from the UK [25] and Switzerland [26] both found no association between area-level SEP and risk of childhood leukemia. The different populations studied may be one potential reason in explaining the inconsistent results. Moreover, negative associations between individual-level family income, mother's education and father's education and risk of childhood leukemia were reported by case-control studies in the North America.[10] Selection bias related to SEP in case-control studies, and

possible distinct associations between different SEP measures and risk of ALL have been discussed to be potential reasons for the heterogeneous results. Pool *et al.* suggested future case-control studies to estimate SEP-related selection and participation so that the influence of the selection bias can be evaluated.[10]

Another previous study examined the association between county-level poverty and risk of leukemia in SEER 17 during 2000-2005: it reported higher incidence rate of leukemia in high-poverty counties among Whites but in low-poverty counties among Blacks, which seemed to be consistent with our findings for Blacks but different for Whites.[12] This may be due to the different classifications of race/ethnicity. Hispanic ethnicity was not separately considered in the previous study. As there are a few Blacks of Hispanic origin, the NH-Blacks in the current study represent similar population as the Blacks in the previous study and consistent results have been found. However, there are a large proportion of Whites who have a Hispanic origin; the observed negative association among Whites in the previous study may be driven by White children of Hispanic origin. Moreover, leukemia other than ALL was studied in the previous study. In addition, census tract-level composite SEP was investigated in the current study while the county-level poverty was used in the previous study. Census tracts are smaller and more homogenous than counties, which can better capture children's socioeconomic environment in a more precise manner.

The positive association between SEP and risk of childhood ALL among NH-Whites, NH-Blacks, APIs, and AIANs supports Greave's delayed infection hypothesis.[8] Specifically, this hypothesis was proposed to explain the etiology of B-cell ALL. B-cell ALL has a peak incidence

at age 1-4 years and its relative proportion decreases with the increase of age. The current study found the association between SEP and risk of ALL varied by age, with the magnitude of positive association decreased with the increase of age. This supports that the delayed infection hypothesis may explain the potential etiology for B-cell ALL, but not for T-cell ALL. Statistically significant positive trends were observed among age 1-4 years for all four race groups, and among age 5-9 years for all race groups except AIANs. Marginally significant associations were observed among NH-Blacks and APIs aged 10-14 years, and among NH-Blacks aged 15-19 years. No association was found among NH-Whites aged 10-14 and 15-19 years. Variations in the magnitude of the positive association were also observed across race groups. Among cases diagnosed at age 1-4 years, the magnitude of the association was the largest among AIANs, followed by NH-Blacks, APIs and was the smallest among NH-Whites: comparing children with the highest SEP to the lowest SEP, incidence rate ratios were 2.94 (95% CI, 1.16-7.42), 2.00 (95% CI, 1.41-2.82), 1.85 (95% CI, 1.38-2.50) and 1.53 (95% CI, 1.34-1.76), respectively. Underlying reasons for different magnitudes should be examined.

The observed ethnic difference in the relationship between SEP and risk of ALL might reflect the infection paradox in explaining the etiology of ALL.[27] The infective lymphoid recovery hypothesis postulates that mild infections early in life prime the immune adaptive response, whereas later recurrent infections in childhood provide the conditions for the accumulation of cooperating oncogenic mutations necessary for the promotion of ALL.[27] It may be considered that susceptibility and exposure are two main components for children to develop ALL. Children with genetic susceptible loci and/or unregulated immune system (those who lack exposures to infections in early life) may be considered of high susceptibility; and recurrent infections later in

childhood may be considered as exposure. When there is an excess of one component, less is needed of the other components in order to develop the malignancy. Hispanics have been reported to have high genetic susceptibility to develop ALL, [28] so they may be of high susceptibility to develop ALL regardless of whether their immune system is unregulated or not. We hypothesize that the negative association between SEP and incidence of ALL among Hispanics is due to more recurrent infections later during childhood among Hispanics of low SEP which increase their risk of ALL. The magnitude of the negative association was observed to be larger among Hispanics of older age in the current study. This is also consistent with the above hypothesis as the effect of recurrent infections should be cumulative over time based on the infective lymphoid recovery hypothesis.

ALL diagnosed among infants is usually a very distinct subtype: over two thirds of the infant ALLs involve an *MLL* gene rearrangement.[29] Maternal infections during pregnancy, maternal exposure to Topo II inhibitors that naturally exist in some vegetables and fruits, and exposure to other carcinogenesis have been investigated as potential causal factors.[30, 31] Yet, not a single factor has gained enough evidence to be associated with risk of childhood ALL. Children with medium SEP were observed to have the lowest incidence of ALL, as compared to children of higher or lower SEP, consistently for all race/ethnicity groups. This indicates that whatever triggers the mutation might be the same across race/ethnicity groups, and there might be two distinct causal factors: one associated with high SEP and the other associated with low SEP.

Potential limitations in the SEP measure used in this study should be considered. First, although census tracts are considered to be relatively homogenous, the area-level SEP does not represent

the individual-level SEP; however, area-level SEP captures the neighborhood social and economic conditions which may also influence individual's health susceptibility, especially in small homogeneous areas such as census tracts. Second, the composite SEP index combines several SEP aspects, including working class, unemployment, poverty, income, education and housing, which individually might have a different relationship with risk of ALL; [10, 32] yet data on specific SEP measures are not publically available in SEER data due to confidential issues. Therefore, examination on association between each SEP measure and risk of ALL is limited. Third, the SEP index was assigned to each case based on the census tract of residence at time of diagnosis using census information from the year 2000. Changes in SEP over 2000-2010 cannot be captured. Children's SEP at time of birth, which may be critical for disease susceptibility, cannot be examined. Nevertheless, those limitations should apply to all race/ethnicity groups, thus the observed ethnic difference in the relationship between SEP and risk of ALL is unlikely to be artificial.

Some other limitations should also be considered in interpreting the findings. First, there may be some misclassifications of race/ethnicity. SEER racial/ethnic classifications were reported to have an excellent agreement with self-reported racial classifications, however, except for the AIAN classification.[33] Second, there may be underdiagnosis or underrecording of ALL cases, although population-based cancer registry data were used. It is possible that the degree of underdiagnosis or reporting is differential across race/ethnicity and/or SEP groups. Third, there may be overestimates of the incidence among Hispanics due to underreport of the Hispanic population: some illegal Hispanic immigrants are not documented but they will seek for medical care when their children present with ALL.[34] Last but not the least, as the etiology may differ

between B-cell ALL and T-cell ALL, examining association of SEP and risk of specific subtypes of ALL can provide better information for disease etiology investigation. However, information regarding the subtypes of ALL is limited in SEER data.

In conclusion, the current study is the first and the largest population-based study in the United States to investigate the assocaition between SEP and risk of childhood ALL stratified by race/ethnicity. No subject participation was involved. NH-Whites, NH-Blacks, APIs and AIANs of higher SEP were found to have higher incidence of ALL, while Hispanics of higher SEP had lower incidence of ALL. Future studies should confirm the racial and ethnic differences and examine the underlying reasons for the assocaition between SEP and risk of childhood ALL.

Table 2-1. Crude (Unadjusted) Incidence Rates of Childhood Acute Lymphoblastic Leukemia by SEP, Sex, and Age in each Race/Ethnicity Group, SEER 16 Registries, 2000-2010

	All Children	NH-White	NH-Black	Hispanic	API	AIAN
				Per 100, 000 (95% CI)		
All children	3.43 (3.36-3.50)	3.28 (3.18 - 3.39)	1.70 (1.56 - 1.85)	4.54 (4.39 - 4.70)	2.99 (2.76 - 3.23)	3.04 (2.37 - 3.89)
Sex						
Girl	3.01 (2.92 - 3.12)	2.89 (2.75 - 3.03)	1.45 (1.27 - 1.66)	4.00 (3.80 - 4.22)	2.69 (2.39 - 3.03)	2.63 (1.80 - 3.83)
Boy	3.82 (3.71 - 3.93)	3.65 (3.51 - 3.81)	1.94 (1.73 - 2.17)	5.06 (4.83 - 5.29)	3.27 (2.95 - 3.63)	3.43 (2.48 - 4.76)
Age						
<1 year	2.03 (1.79 - 2.30)	1.91 (1.58 - 2.31)	1.73 (1.16 - 2.58)	2.28 (1.86 - 2.79)	2.19 (1.46 - 3.30)	1.06 (0.15 - 7.56)
1-4 years	7.82 (7.57 - 8.07)	8.33 (7.96 - 8.72)	3.27 (2.83 - 3.78)	8.97 (8.51 - 9.46)	7.07 (6.31 - 7.93)	6.77 (4.58 - 10.02)
5-9 years	3.42 (3.27 - 3.57)	3.23 (3.03 - 3.45)	1.66 (1.39 - 1.98)	4.53 (4.22 - 4.85)	3.20 (2.74 - 3.73)	2.91 (1.72 - 4.91)
10-14 years	2.09 (1.98 - 2.20)	1.79 (1.65 - 1.95)	1.42 (1.19 - 1.71)	3.03 (2.78 - 3.29)	1.65 (1.34 - 2.04)	2.35 (1.36 - 4.04)
15-19 years	1.72 (1.62 - 1.82)	1.48 (1.35 - 1.62)	0.90 (0.71 - 1.14)	2.72 (2.48 - 2.98)	1.16 (0.91 - 1.48)	1.73 (0.93 - 3.22)
SEP						
Lowest	3.40 (3.25 - 3.56)	2.81 (2.55 - 3.09)	1.42 (1.23 - 1.65)	4.94 (4.67 - 5.23)	2.24 (1.73 - 2.89)	2.07 (1.30 - 3.28)
Low	3.53 (3.37 - 3.70)	3.15 (2.91 - 3.40)	1.82 (1.53 - 2.16)	4.85 (4.54 - 5.19)	2.32 (1.85 - 2.92)	3.78 (2.41 - 5.92)
Median	3.31 (3.15 - 3.48)	3.10 (2.89 - 3.34)	1.82 (1.49 - 2.23)	4.36 (4.02 - 4.73)	3.01 (2.52 - 3.61)	3.02 (1.63 - 5.62)
High	3.30 (3.13 - 3.47)	3.34 (3.12 - 3.56)	1.96 (1.55 - 2.48)	3.90 (3.51 - 4.32)	2.93 (2.48 - 3.46)	3.08 (1.47 - 6.47)
Highest	3.52 (3.35 - 3.69)	3.60 (3.40 - 3.82)	2.24 (1.66 - 3.04)	3.29 (2.88 - 3.77)	3.65 (3.21 - 4.15)	4.88 (2.19 - 10.86)
Unknown	4.62 (3.92 - 5.44)	4.77 (3.86 - 5.89)	1.64 (0.74 - 3.65)	6.33 (4.63 - 8.67)	3.11 (1.62 - 5.97)	15.14 (4.88 - 46.93)

Abbreviation: SEP, socioeconomic position; 95% CI, 95% confidence interval; NH-White, non-Hispanic-White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.

Table 2-2. Adjusted Incidence Rate Ratios of Childhood Acute Lymphoblastic Leukemia by SEP and Race/Ethnicity, SEER 16 Registries, 2000-2010

	SEP					
	Lowest	**Low**	**Median**	**High**	**Highest**	**P-trend**
Race/Ethnicity	[a]Adjusted Incidence Rate Ratio (95% CI)					
NH-White	1.00	1.12 (0.99 - 1.26)	1.10 (0.98 - 1.24)	1.19 (1.06 - 1.33)	1.29 (1.15 - 1.44)	<.001
NH-Black	1.00	1.29 (1.03 - 1.62)	1.31 (1.02 - 1.68)	1.43 (1.08 - 1.89)	1.67 (1.20 - 2.34)	<.001
Hispanic	1.00	0.99 (0.91 - 1.08)	0.90 (0.81 - 0.99)	0.81 (0.72 - 0.91)	0.70 (0.60 - 0.81)	<.001
API	1.00	1.02 (0.73 - 1.44)	1.32 (0.96 - 1.80)	1.26 (0.93 - 1.72)	1.57 (1.17 - 2.09)	<.001
AIAN	1.00	1.84 (0.97 - 3.51)	1.48 (0.68 - 3.21)	1.53 (0.64 - 3.67)	2.46 (0.98 - 6.19)	0.085

Abbreviation: SEP, socioeconomic position; 95% CI, 95% confidence interval; NH-White, non-Hispanic-White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.
[a]Adjusted for sex, age and year of diagnosis.

Table 2-3. Adjusted Incidence Rate Ratios of Childhood Acute Lymphoblastic Leukemia by SEP, Age, and Race/Ethnicity, SEER 16 Registries, 2000-2010

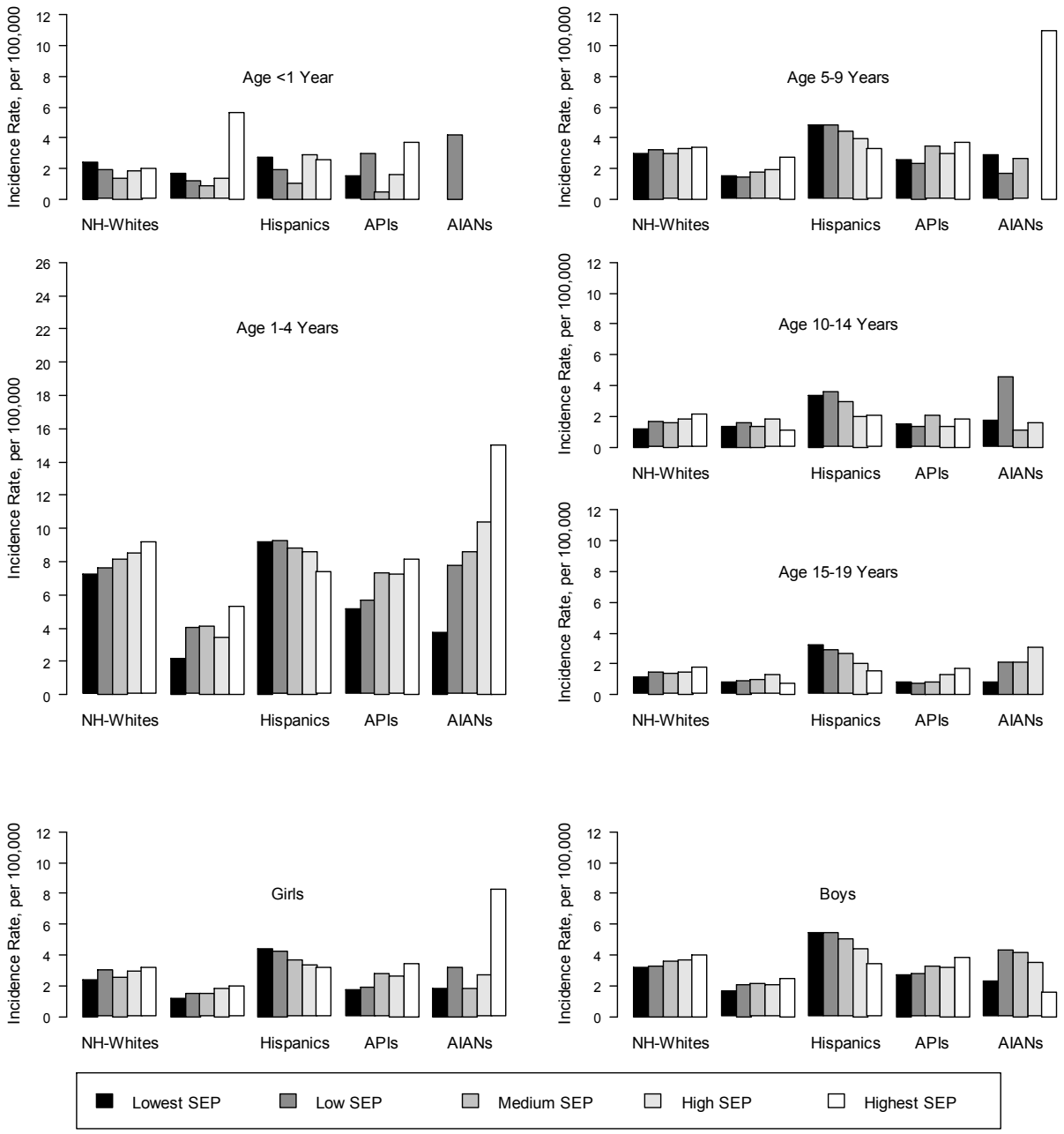
	SEP					
	Lowest	**Low**	**Median**	**High**	**Highest**	**P-trend**
Age<1 year	[a]Adjusted Incidence Rate Ratio (95% CI)					
NH-White	1.00	0.88 (0.61 - 1.29)	0.56 (0.35 - 0.88)	1.07 (0.72 - 1.58)	1.33 (0.91 - 1.93)	0.184
NH-Black	1.00	1.02 (0.67 - 1.56)	0.66 (0.40 - 1.09)	1.29 (0.81 - 2.06)	1.72 (1.05 - 2.82)	0.027
Hispanic	1.00	0.78 (0.54 - 1.13)	0.45 (0.29 - 0.70)	0.72 (0.49 - 1.07)	0.70 (0.48 - 1.04)	0.093
API	1.00	0.81 (0.49 - 1.34)	0.66 (0.39 - 1.14)	1.14 (0.70 - 1.84)	1.60 (1.01 - 2.54)	0.031
AIAN	1.00	1.46 (0.70 - 3.05)	0.75 (0.31 - 1.82)	1.39 (0.54 - 3.59)	2.54 (0.94 - 6.84)	0.105
Age 1-4 years						
NH-White	1.00	1.18 (1.02 - 1.37)	1.28 (1.11 - 1.47)	1.41 (1.22 - 1.62)	1.53 (1.34 - 1.76)	<.001
NH-Black	1.00	1.36 (1.07 - 1.73)	1.52 (1.17 - 1.97)	1.69 (1.27 - 2.26)	2.00 (1.41 - 2.82)	<.001
Hispanic	1.00	1.04 (0.93 - 1.17)	1.03 (0.91 - 1.17)	0.95 (0.82 - 1.09)	0.81 (0.69 - 0.96)	0.023
API	1.00	1.09 (0.76 - 1.55)	1.53 (1.11 - 2.11)	1.49 (1.09 - 2.05)	1.85 (1.38 - 2.50)	<.001
AIAN	1.00	1.95 (1.02 - 3.73)	1.72 (0.79 - 3.74)	1.82 (0.76 - 4.39)	2.94 (1.16 - 7.42)	0.028
Age 5-9 years						
NH-White	1.00	1.08 (0.91 - 1.28)	1.07 (0.90 - 1.26)	1.14 (0.97 - 1.35)	1.20 (1.02 - 1.41)	0.017
NH-Black	1.00	1.25 (0.97 - 1.61)	1.27 (0.96 - 1.67)	1.38 (1.02 - 1.87)	1.56 (1.09 - 2.23)	0.004
Hispanic	1.00	0.96 (0.83 - 1.10)	0.86 (0.74 - 1.01)	0.77 (0.65 - 0.91)	0.64 (0.53 - 0.77)	<.001
API	1.00	0.99 (0.69 - 1.43)	1.28 (0.91 - 1.79)	1.22 (0.87 - 1.69)	1.45 (1.07 - 1.98)	0.003
AIAN	1.00	1.78 (0.93 - 3.43)	1.44 (0.66 - 3.14)	1.49 (0.62 - 3.59)	2.30 (0.91 - 5.84)	0.115
Age 10-14 years						
NH-White	1.00	1.13 (0.93 - 1.37)	0.99 (0.81 - 1.21)	0.97 (0.79 - 1.18)	1.10 (0.91 - 1.33)	0.809
NH-Black	1.00	1.30 (0.99 - 1.70)	1.18 (0.88 - 1.58)	1.17 (0.85 - 1.61)	1.43 (0.99 - 2.07)	0.073
Hispanic	1.00	1.00 (0.84 - 1.19)	0.80 (0.66 - 0.97)	0.65 (0.53 - 0.80)	0.59 (0.47 - 0.72)	<.001
API	1.00	1.04 (0.71 - 1.51)	1.19 (0.83 - 1.68)	1.03 (0.73 - 1.46)	1.33 (0.96 - 1.85)	0.087
AIAN	1.00	1.86 (0.96 - 3.60)	1.34 (0.61 - 2.94)	1.26 (0.52 - 3.06)	2.11 (0.83 - 5.38)	0.237
Age 15-19 years						
NH-White	1.00	1.04 (0.85 - 1.28)	0.96 (0.78 - 1.18)	0.98 (0.80 - 1.21)	1.05 (0.86 - 1.30)	0.868
NH-Black	1.00	1.20 (0.91 - 1.59)	1.14 (0.84 - 1.54)	1.18 (0.85 - 1.65)	1.37 (0.94 - 2.00)	0.089
Hispanic	1.00	0.92 (0.76 - 1.11)	0.78 (0.64 - 0.95)	0.66 (0.53 - 0.82)	0.56 (0.44 - 0.71)	<.001
API	1.00	0.96 (0.66 - 1.40)	1.15 (0.80 - 1.64)	1.04 (0.73 - 1.49)	1.27 (0.91 - 1.78)	0.106
AIAN	1.00	1.72 (0.89 - 3.34)	1.29 (0.59 - 2.86)	1.28 (0.52 - 3.11)	2.02 (0.79 - 5.16)	0.244

Abbreviation: SEP, socioeconomic position; 95% CI, 95% confidence interval; NH-White, non-Hispanic-White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.
[a]Adjusted for sex and year of diagnosis.

Supplementary Table 2-1. Crude (Unadjusted) Incidence Rates of Childhood Acute Lymphoblastic Leukemia by SEP and Race/Ethnicity, Stratified by Age and by Sex, SEER 16 Registries, 2000-2010

	NH-White	NH-Black	Hispanic	API	AIAN
			Per 100, 000 (95% CI)		
Age<1 year old					
Lowest	2.43 (1.55 - 3.81)	1.68 (0.90 - 3.13)	2.74 (2.00 - 3.77)	1.52 (0.38 - 6.07)	__
Low	1.92 (1.24 - 2.97)	1.19 (0.45 - 3.17)	1.96 (1.27 - 3.04)	3.02 (1.26 - 7.26)	4.21 (0.59 - 29.91)
Median	1.40 (0.86 - 2.29)	0.89 (0.22 - 3.55)	1.08 (0.54 - 2.16)	0.49 (0.07 - 3.51)	__
High	1.89 (1.25 - 2.84)	1.36 (0.34 - 5.45)	2.93 (1.76 - 4.86)	1.65 (0.62 - 4.39)	__
Highest	2.01 (1.36 - 2.97)	5.66 (2.12 - 15.07)	2.59 (1.35 - 4.98)	3.73 (2.07 - 6.74)	__
Age 1-4 years old					
Lowest	7.25 (6.33 - 8.29)	2.20 (1.68 - 2.89)	9.21 (8.43 - 10.07)	5.14 (3.47 - 7.61)	3.78 (1.70 - 8.41)
Low	7.64 (6.83 - 8.54)	4.02 (3.08 - 5.25)	9.26 (8.35 - 10.27)	5.66 (4.07 - 7.89)	7.76 (3.70 - 16.28)
Median	8.18 (7.38 - 9.06)	4.13 (3.00 - 5.67)	8.82 (7.78 - 10.00)	7.36 (5.68 - 9.55)	8.58 (3.57 - 20.61)
High	8.49 (7.72 - 9.34)	3.47 (2.26 - 5.32)	8.63 (7.40 - 10.07)	7.24 (5.72 - 9.17)	10.42 (3.91 - 27.77)
Highest	9.16 (8.39 - 9.99)	5.32 (3.26 - 8.68)	7.38 (6.02 - 9.04)	8.17 (6.74 - 9.91)	15.04 (4.85 - 46.64)
Age 5-9 years old					
Lowest	2.99 (2.45 - 3.64)	1.51 (1.13 - 2.02)	4.80 (4.28 - 5.38)	2.58 (1.56 - 4.29)	2.90 (1.30 - 6.45)
Low	3.24 (2.77 - 3.79)	1.43 (0.96 - 2.11)	4.82 (4.22 - 5.50)	2.35 (1.46 - 3.78)	1.72 (0.43 - 6.87)
Median	2.97 (2.56 - 3.46)	1.75 (1.15 - 2.66)	4.43 (3.76 - 5.21)	3.44 (2.43 - 4.87)	2.65 (0.66 - 10.59)
High	3.32 (2.91 - 3.80)	1.90 (1.16 - 3.10)	3.96 (3.20 - 4.89)	2.97 (2.12 - 4.15)	__
Highest	3.39 (3.01 - 3.81)	2.78 (1.58 - 4.90)	3.30 (2.49 - 4.38)	3.74 (2.91 - 4.79)	10.97 (3.54 - 34.02)
Age 10-14 years old					
Lowest	1.19 (0.88 - 1.61)	1.34 (0.99 - 1.81)	3.38 (2.94 - 3.89)	1.54 (0.83 - 2.87)	1.73 (0.65 - 4.62)
Low	1.66 (1.35 - 2.05)	1.59 (1.11 - 2.28)	3.56 (3.04 - 4.16)	1.31 (0.71 - 2.44)	4.55 (2.05 - 10.14)
Median	1.60 (1.31 - 1.94)	1.34 (0.85 - 2.10)	2.92 (2.39 - 3.56)	2.03 (1.31 - 3.15)	1.13 (0.16 - 8.01)
High	1.80 (1.51 - 2.14)	1.80 (1.14 - 2.86)	2.02 (1.52 - 2.68)	1.34 (0.82 - 2.19)	1.59 (0.22 - 11.32)
Highest	2.11 (1.83 - 2.44)	1.08 (0.48 - 2.40)	2.05 (1.49 - 2.83)	1.84 (1.30 - 2.62)	__
Age 15-19 years old					
Lowest	1.14 (0.86 - 1.50)	0.80 (0.54 - 1.18)	3.20 (2.76 - 3.71)	0.80 (0.36 - 1.79)	0.85 (0.21 - 3.40)
Low	1.50 (1.21 - 1.85)	0.93 (0.58 - 1.50)	2.90 (2.43 - 3.47)	0.76 (0.36 - 1.60)	2.13 (0.69 - 6.61)
Median	1.38 (1.12 - 1.71)	0.97 (0.56 - 1.67)	2.67 (2.15 - 3.30)	0.85 (0.44 - 1.63)	2.13 (0.53 - 8.52)
High	1.47 (1.21 - 1.79)	1.29 (0.73 - 2.27)	2.06 (1.54 - 2.76)	1.32 (0.81 - 2.16)	3.10 (0.78 - 12.39)
Highest	1.75 (1.47 - 2.07)	0.78 (0.29 - 2.08)	1.52 (1.01 - 2.29)	1.71 (1.16 - 2.54)	__
Girls					
Lowest	2.39 (2.07 - 2.78)	1.19 (0.94 - 1.49)	4.43 (4.07 - 4.83)	1.74 (1.15 - 2.65)	1.85 (0.93 - 3.70)
Low	3.01 (2.69 - 3.36)	1.54 (1.18 - 2.01)	4.25 (3.84 - 4.71)	1.87 (1.30 - 2.69)	3.22 (1.61 - 6.44)
Median	2.58 (2.30 - 2.89)	1.50 (1.09 - 2.06)	3.66 (3.22 - 4.15)	2.76 (2.11 - 3.61)	1.83 (0.59 - 5.67)
High	2.94 (2.66 - 3.25)	1.86 (1.31 - 2.63)	3.33 (2.84 - 3.91)	2.63 (2.05 - 3.39)	2.68 (0.86 - 8.31)
Highest	3.17 (2.89 - 3.46)	1.98 (1.25 - 3.15)	3.18 (2.61 - 3.87)	3.44 (2.85 - 4.16)	8.25 (3.43 - 19.81)
Boys					
Lowest	3.20 (2.82 - 3.63)	1.66 (1.37 - 2.01)	5.42 (5.03 - 5.85)	2.71 (1.95 - 3.75)	2.28 (1.22 - 4.23)
Low	3.28 (2.95 - 3.64)	2.09 (1.67 - 2.62)	5.42 (4.97 - 5.92)	2.75 (2.06 - 3.69)	4.32 (2.39 - 7.80)
Median	3.60 (3.28 - 3.96)	2.12 (1.64 - 2.76)	5.03 (4.53 - 5.60)	3.25 (2.55 - 4.14)	4.20 (2.00 - 8.80)
High	3.71 (3.40 - 4.05)	2.05 (1.49 - 2.84)	4.44 (3.87 - 5.08)	3.21 (2.57 - 4.01)	3.48 (1.30 - 9.26)
Highest	4.02 (3.72 - 4.34)	2.49 (1.67 - 3.71)	3.40 (2.82 - 4.10)	3.85 (3.23 - 4.58)	1.60 (0.23 - 11.39)

Abbreviation: SEP, socioeconomic position; 95% CI, 95% confidence interval; NH-White, non-Hispanic-White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.
"-- ": Not estimatable due to limited number of cases



Note: Missing bars were due to limited number of cases in those categories.

Incidence rates were crude (unadjusted).

Figure 2-1. Crude (Unadjusted) Incidence Rates of Childhood Acute Lymphoblastic Leukemia by SEP and Race/Ethnicity, Stratified by Age and by Sex, SEER 16 Registries, 2000-2010

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CHAPTER 3: DIFFERENTIAL INEQUALITY TRENDS OVER TIME IN SURVIVAL AMONG US CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA BY RACE/ETHNICITY, AGE AT DIAGNOSIS AND SEX

3.1 INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common childhood cancer in the United States, [1] and one of the most curable cancers. Treatment advances, such as the introduction of combination chemotherapy and effective treatment for subclinical central nervous system (CNS) leukemia in the 1960s, and the development of risk-based therapy placed on well-designed clinical trials in the 1980s, [2] have contributed to dramatic improvements in survival among children with ALL. The overall 5-year survival probability improved from less than 10% in early 1960s [1] to over 80% in late 1990s.[3] Despite milestones in survival improvements, previous studies identified continuing inequalities in childhood ALL survival, with adverse prognosis reported in Blacks, Hispanics, American Indian/Alaska Natives (AIANs), children aged <1 and 10-19 years at diagnosis, and boys.[4-7]

In the 1990's and 2000's, ALL survival further improved following several medical advances: better precision in treatment with applications of molecular biological tools; [2] a uniform system of risk classification; [8] and the merging in 2000 of the Children's Cancer Study Group and the Pediatric Oncology Group (POG) into the Children's Oncology Group (COG), providing advanced care for over 90% of US childhood cancer patients [9] and two thirds of childhood ALL patients.[10] Consequently, in 2000-04, children diagnosed with ALL at 0-14 years in the US are reported to have an overall 5-year survival probability of 87.5% as compared to 80.2% in 1990-94.[11]

With continued treatment and survival improvement, several studies have reported decreased inequality in survival among Blacks and Whites. For patients enrolled in COG trials, the hazard ratio of all-cause mortality in Blacks relative to Whites aged 0-21 years was reported to drop from 1.73 in 1990-94 to 1.37 in 2000-05.[10] A population-based study also reported narrowed gap in survival between Blacks and Whites: 5-year survival rates for Blacks and Whites, respectively, increased from 56.6% and 76.3% in 1981-1990 to 86.1% and 88.9% in 2001-10.[12] However, research is limited regarding how the inequalities in survival among children of other race/ethnicity groups (Hispanics, Asian/Pacific Islanders (APIs), and AIANs) as compared to Whites have changed over time, and whether racial/ethnic inequalities in survival vary by age at diagnosis and sex.

The current study sought to determine how inequalities in survival after childhood ALL by race/ethnicity have changed over the period 1975-2010 and describe the inequality in survival among US children with ALL by race/ethnicity, age at diagnosis and sex in the period 2000-10.

3.2 METHODS

3.2.1 Study population

Data were obtained from the original nine population-based cancer registries in the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results program (SEER 9). The SEER 9 registries collected information from nine selected states or metropolitan areas (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) in the United States since 1973, covering approximately 10% of the US population.[13]

The SEER 9 registries were selected for this analysis over SEER 13 or 18 registries in order to compare historical trends of the same population starting from the 1970s. Cases diagnosed in 1973 and 1974 were not included because the Seattle-Puget Sound and Atlanta registries joined the SEER program in 1974 and 1975, respectively. Children diagnosed at age 0 to 19 years with a first primary malignant ALL during 1975-2010 in SEER 9 registries were included. ALL cases were ascertained according to the International Classification of Diseases for Oncology, Third Edition.[14] Six cases identified through autopsy/death certificate, and 47 cases with missing race/ethnicity information were also excluded.

Race and Hispanic ethnicity data in SEER registries are generally derived from information abstracted from patients' medical records and is mainly based on self- or caregiver-report, but may be based on medical staff observation.[15] Hispanic identification was additionally enhanced using the North American Association for Central Cancer Registries Hispanic-Latino identification algorithm,[16] which is based on surnames and birthplace. Mutually-exclusive racial/ethnic categories were defined as: Hispanics, non-Hispanic-Whites (NH-Whites), non-Hispanic-Blacks (NH-Blacks), APIs, and AIANs. Four diagnosis periods (1975-83, 1984-91, 1992-99 and 2000-10) were selected to capture relevant secular trends in treatment improvements and to allow sufficient follow-up for reliable estimates. Age at diagnosis was categorized as <1, 1-9 and 10-19 years, based on NCI's risk classification for ALL.[8]

Follow-up for vital status is conducted by the SEER cancer registries using linkages to national and state vital statistics records. Follow-up in this study was through the end of 2011, with a median follow-up of 8.9 years. Death due to ALL (ALL mortality) was the primary outcome of

interest, which was ascertained based on the SEER cause-specific death classification.[17] Cases who were alive during the follow-up were censored at the last active follow-up. Those who died of causes not attributable to ALL had their at-risk status terminated on the date of death. Death due to all causes was analyzed as the secondary outcome (Supplementary Table 3-1 and 3-2).

3.2.2 Statistical analyses

Characteristics of cases were tabulated and compared among the five race/ethnicity groups, using chi-square tests. Cumulative ALL mortalities among cases and their 95% confidence intervals (CIs) were estimated using the cumulative incidence function.[18] Multivariable Cox regression was applied to estimate ALL mortality hazard ratios (HRs) and their 95% CIs associated with race/ethnicity, sex, and age at diagnosis, adjusting for each other, stratified by diagnosis period. The age-specific HRs adjusting for sex, and sex-specific HRs adjusting for age, associated with race/ethnicity, stratified by diagnosis period were also analysed using multivariable Cox regression. Tests of a linear trend in the change of inequalities with respect to a variable (e.g., race/ethnicity) over time were performed by treating the four-category diagnosis period variable as continous in the interaction term of the diagnosis period and the variable in the Cox regression models. Proportional hazard assumptions were checked using scaled Schoenfeld residuals [19] by 'estat phtest' command in Stata and confirmed. Kaplan-Meier methods were used to estimate the overall survival. Two-sided P-values (P) were reported and those less than 0.05 were considered as statistically significant. Stata, version 12.0 was used for all analyses, except for the cumulative incidence calculation which was done in SAS, version 9.4. Cumulative incidence curves were plotted using R, version 2.13.1.

3.3 RESULTS

A total of 7365 children were included and their characteristics by race/ethnicity are shown in **Table 3-1**. The study population comprised of 67.9% of NH-Whites, 14.9% Hispanics, 8.5% APIs, 7.2% NH-Blacks and 1.5% AIANs, with a noticeable increase in the relative proportion of Hispanic cases, from 8.8% of all childhood ALL cases in 1975-83 to 21.6% in 2000-10; the proportions of other race/ethnicity groups had less change. Sex was distributed similarly across race/ethnicity groups (P=0.639), with more boys with ALL. The age distribution varied by race/ethnicity (P=0.002): about 70% of NH-Whites and Hispanics, 64.9% of NH-Blacks, 76.7% of APIs, and 73.9% of AIANs were diagnosed at 1-9 years old.

Among all children with ALL, the 5-year cumulative ALL mortality decreased from 35% in 1975-83 to 10% in 2000-10. **Table 3-2** shows the 5-year cumulative ALL mortalities by race/ethnicity, age at diagnosis, and sex within each diagnosis period. **Figure 3-1** compares cumulative ALL mortality curves across race/ethnicity groups in each diagnosis period, which illustrates the change in inequalities of ALL mortality among different race/ethnicity groups over the four diagnosis periods.

Cumulative ALL mortalities reduced over time for children of any race/ethnicity, age at diagnosis, and sex; however, improvement patterns and magnitudes varied, leading to changes in inequalities. As compared with NH-Whites, NH-Blacks historically had worse survival. The absolute inequality in 5-year cumulative ALL mortality increased from 15% (48% in NH-Blacks vs. 33% in NH-Whites) in 1975-83 to 23% (43% vs. 20%) in 1984-91, but decreased later to 3% (11% vs. 8%) in 2000-10. For Hispanics, the absolute inequality in 5-year cumulative incidence

of ALL mortality changed from 10% (43% in Hispanic vs. 33% in NH-White) in 1975-83 to 7% (15% vs. 8%) in 2000-10. Historically, APIs with ALL fared as well as NH-Whites, but AIANs fared worse: with a 5-year cumulative ALL mortality of 8% (95% CI, 7%-10%) in NH-Whites, 10% (95% CI, 7%-15%) in APIs, and 19% (95% CI, 8%-32%) in AIANs in 2000-10. Inequalities in overall 5-year survival probabilities showed the same pattern as cumulative ALL mortalities (**Supplementary Table 2-1**). The overall 5-year survival probability increased from 61% in 1975-83 to 88% in 2000-10 among all children with ALL.

Girls had better survival than boys historically. The 5-year cumulative mortality decreased from 30% (95% CI, 26%-33%) in 1975-83 to 9% (95% CI, 7%-11%) in 2000-10 in girls, and from 39% (95 CI, 35%-42%) to 11% (95 CI, 10%-13%) in boys. Children diagnosed with ALL at 1-9 years old had better survival than <1 and 10-19 years old, such inequality persisted in magnitude in 2000-10, with a 5 year cumulative ALL mortality of 5% (95% CI, 4%-7%), 20% (95% CI, 17%-23%) and 31% (95% CI, 21%-41%) in children aged 1-9, 10-19 and <1 year, respectively.

Table 3-3 shows the adjusted ALL mortality HRs for race/ethnicity, sex, and age at diagnosis by diagnosis period. Compared to NH-Whites, after adjusting for age at diagnosis and sex: the HR in NH-Blacks increased from 1.46 (95% CI, 1.09-1.94) in 1975-83 to 2.09 (95% CI, 1.57-2.79) in 1984-91, and then dropped to 1.21 (95% CI, 0.74-1.96) in 2000-10; the HR in Hispanics steadily increased (P=0.023) from 1.28 (95% CI, 0.98-1.66) in 1975-83 to 1.95 (95% CI, 1.48, 2.58) in 2000-10; the HR in APIs changed (P=0.275) from 1.05 (95% CI, 0.76-1.46) in 1975-83 to 1.37 (95% CI, 0.91-2.08) in 2000-10; the HR for AIANs was 1.26 (95% CI, 0.60-2.65) in 1975-83 and increased to 2.19 (95% CI, 1.28-3.75) in 1984-91, with a remaining high HR of

2.28 (95% CI, 1.11-4.67) in 2000-10. Similar results were observed when all-cause mortality was analyzed as the outcome (**Supplementary Table 3-2**).

Age-specific and sex-specific HRs for race/ethnicity by diagnosis period are shown in **Table 3-4**. Similar racial/ethnic inequalities trends were observed in each age at diagnosis group, and among boys and girls. However, racial/ethnic inequalities varied by age at diagnosis and by sex. The racial/ethnic inequalities were the largest among age 1-9 years except for AIANs. In 2000-10, NH-Blacks and APIs diagnosed at 1-9 years old had HRs of 1.9 (95% CI, 0.93-3.89) and 2.02 (95% CI, 1.10-3.69) relative to NH-White counterparts, respectively. API boys had an HR of 1.61 (95% CI, 1.00-2.60) relative to NH-White boys in 2000-10, such inequality was not observed among girls. In contrast, in 2000-10, the inequality was larger among Hispanic girls than boys as compared to their NH-White counterparts, with HRs of 3.01 (95% CI, 1.96-4.64) and 1.43 (95% CI, 0.99-2.08) in Hispanic girls and boys respectively.

After adjusting for sex and race/ethnicity, children aged <1 and 10-19 years at diagnosis had HRs of 7.57 (95% CI, 4.85-11.80) and 4.01 (95% CI, 3.09-5.19) relative to those aged 1-9 years, respectively, in 2000-10 which increased from HRs of 3.60 (95% CI, 2.57-5.05) and 2.04 (95% CI, 1.73-2.41), respectively, in 1975-83. After adjusting for age at diagnosis and race/ethnicity, boys consistently had higher hazards of ALL mortality than girls over four diagnosis periods (adjusted HR=1.32, 95% CI, 1.01-1.72, in 2000-10).

3.4 DISCUSSION

Treatment advance in curing most children with ALL has been considered as one of the greatest successes in the history of cancer research. Yet, not all subgroups benefit equally. This study documents the inequality trends over time by race/ethnicity, age at diagnosis and sex, based on ALL cases from SEER 9 registries over 3.5 decades. Cumulative ALL mortality, overall survival probability, and adjusted ALL mortality hazard ratios have been reported, as choices of outcome measures and scales of inequality can influence the measurements and interpretations of survival inequality trends. This study also highlights several racial/ethnic inequalities in survival among certain age and sex subgroups of children with ALL in the period 2000-10.

Overall, we found that as compared to NH-Whites, the relative inequalities in ALL mortality decreased in NH-Blacks, but increased over time in other minority groups (Hispanics, APIs, and AIANs), significantly among Hispanics. In 2000-10, NH-Blacks diagnosed at 1-9 years old, Hispanics diagnosed at 1-9 and 10-19 years old, APIs diagnosed at 1-9 years old and AIANs diagnosed at 10-19 years old had about twice the hazard rates of ALL mortality than their NH-White counterparts diagnosed at the same age group. Moreover, larger inequalities were observed among Hispanic girls than boys, and inequality was observed only among API boys but not girls, as compared to their NH-White counterparts.

Survival inequality between NH-Blacks and NH-Whites was the highest between 1984 and 1991 and then declined afterwards. These differences for 1984-1991are illustrated in Figure 3-1 and are the result of substantial improvement in survival among NH-Whites but limited improvement in NH-Blacks from the preceding period. These observations may suggest that advances in

therapy were more easily accessed by the NH-White children as compared with their NH-Black counterparts. The decreasing inequality observed between NH-Whites and NH-Blacks is consistent with previous findings.[10, 12] In 2000-10, NH-Blacks had 3% higher in absolute values of 5-year cumulative ALL mortality and an adjusted ALL mortality HR of 1.21 which did not differ statistically from NH-Whites. Previously, Hunger *et al.* reported narrowed inequality between White and Black patients enrolled in COG trials, and they reported all-cause mortality as opposed to ALL-specific mortality.[10] Our population-based study allows us to better generalize our results to the US population, especially considering that access to care and enrollment in clinical trials is usually an important driver of mortality differences. Another recent study reported a significantly narrowed gap in 5-year relative survival between Whites and Blacks diagnosed with ALL at 0-14 years.[12] However, this study included ALL cases in SEER 18 registries so the secular trends might be impacted by the appreciable changes in the SEER population, starting with the 9 registries in 1975, which we studied in this report for consistency over time, to 18 registries in 2000.

Blacks are known to have a higher incidence of the T-cell subtype of ALL as compared to Whites, which in general has a worse prognosis; [7, 10] however, ALL immunophenotype information is limited in SEER data. The "grade" variable in SEER data shows immunophenotype information for leukemia. However, the use of this variable is cautioned, especially for cases diagnosed in 1973-2000 due to the change of reporting requirements and medical terminology over time. Moreover, for cases included in the current study, the immunophenotype information is missing for more than half of the cases. Treatment improvement, e.g., the application of more intensive treatment protocols, and the approval of

Nelarabine for patients with recurring T-cell ALL in 2000,[2] may have contributed to the closing gap between Blacks and Whites.[10] For children treated at St Jude Children's Research Hospital, where patients were treated with contemporary multimodality therapy according to therapeutic protocols regardless of race, ethnicity, or ability or pay for their medical care, no difference was found in survival of Blacks as compared to Whites in treatment eras from 1984 through 2007.[20, 21] This supports the hypothesis that, with equal access to contemporary, risk-based treatment, there is likely no Black-White inequality in ALL mortality. However, NH-Blacks diagnosed at 1-9 years old have still been observed to have an adjusted ALL mortality HR of 1.90 (95% CI, 0.93-3.89) in 2000-10 relative to the NH-White counterpart in the current study, which needs attention in future studies as to identify reasons and interventions.

There was a statistically significantly widening trend in the relative inequalities in ALL mortality hazards between Hispanics and NH-Whites. This shows that, as a group, the relative improvement following ALL treatment advances has been slower in Hispanics than in NH-Whites. An important factor in interpreting this result is the change in the US Hispanic population in the study regions over the study time period. The proportion of Hispanic cases in our study population increased from 8.8% in 1975-83 to 21.6% in 2000-10, primarily due to immigration. In some, but not all, of the 9 SEER registries, we found statistically significant or marginally significant increasing trends in inequalities among Hispanics as compared to NH-Whites (**Supplementary Table 3-3)**. These registries were Atlanta, San Francisco and Utah Registries, among which the relative proportion of Hispanic population increased substantially over time to exceed 20% in 2000-10 (**Supplementary Table 3-4)**. No change in the relative inequality was observed in the other registries. The supplementary analysis, although limited in

power, may indicate that recent Hispanic immigrants may be more vulnerable to the relative inequality and may not be benefitting as much from the advances of the ALL treatment. Previous reports have shown decreasing education level among Hispanics due to immigration,[22] and non-adherence to the treatment among illegal immigrant Mexican and first-generation Mexican-American children,[23] which may contribute to worse survival, though the association between socioeconomic status and the survival of ALL is not conclusive. The heterogeneity of Hispanics (e.g., Mexican, Puerto Rican, and Cuban) also complicates the interpretation of the inequality trend if the ethnic composition has changed over time. Regardless of possible explanations, the widening relative inequality is of concern and requires attention by healthcare providers and researchers. Moreover, the larger inequalities between NH-Whites and Hispanics observed among girls (HR=3.01) than boys (HR=1.43) require future investigation and sex difference should be considered in identifying potential reasons of the inequalities.

APIs had similar survival as NH-Whites historically, as consistent with previous studies.[5] However, albeit non-significant, relative inequalities between APIs and NH-Whites grew over time, especially among cases diagnosed at age 1-9 years. Moreover, the current study found APIs aged 1-9 years had over two-fold ALL mortality hazard (95% CI, 1.10-3.69), and API boys had an HR of 1.61 (95% CI, 1.00-2.60), relative to their NH-White counterparts in 2000-10. The worse survival among APIs as compared to NH-Whites in specific age and sex subgroups has never been reported before. Variations among API subgroups in childhood ALL survival has been reported, with Vietnamese and Filipinos faring significantly worse than NH-Whites.[24] Unfortunately, as with Hispanics, the small number of ALL cases limited analyses of distinct API ethnic groups. We found that a large inequality between AIANs and NH-Whites persisted

over time. Results on AIANs should be interpreted with caution, as there were only 111 AIAN cases in the current study. However, this study is to our knowledge the largest and the first study that documents the trend of inequalities between AIANs and NH-Whites in ALL survival over time.

Sex differences in ALL survival are partially explained by sex differences in the distributions of ALL immunophenotype and DNA index.[6] Higher mortality among boys than girls persisted over the time period (HRs around 1.3). However, treatment advance has decreased absolute inequality in the cumulative ALL mortality between boys and girls.

Growing relative inequalities in mortality have been observed over time across age groups: infants and children diagnosed at 10-19 years old, infants in particular, who have much more room to improve, have actually improved relatively slower than children aged 1-9 years. This highlights the success in the treatment of children aged 1-9 years and the difficulties in improving the survival of infants and 10-19 year olds. Approximately 80% of infants with ALL have an *MLL* gene rearrangement which is associated with poor prognosis.[25] Several treatment strategies such as the use of stem-cell transplantation in first remission and treatment intensification have been explored in clinical trials but have not yet resulted in significant improvement in survival.[25, 26] Children diagnosed at 10-19 years old are less likely to enroll in pediatric trials than children diagnosed at 1-9 years old.[10] These may be, at least partly, associated with the fewer improvements have been made for treating infants and adolescents with ALL. Even though children diagnosed with ALL at age 1-9 years old have the best prognosis and experience the most treatment advances and survival improvement compared to

children diagnosed at other age groups, the racial/ethnic inequalities between NH-Whites and other minority groups (NH-Blacks, Hispanics, and APIs) have been observed to be the largest among them.

Although our population-based analyses do not include data that allow us to examine specific underlying causes of these differences in survival by race/ethnicity, possible explanations include both biological and sociocultural causes. Pollock *et al*. found African-Americans enrolled in POG clinical trials presented with worse disease presentations (e.g., higher white blood cell (WBC) counts, and common ALL antigen) than Whites which were associated with subsequent treatment failures.[7] Genomic rearrangement of *cytokine receptor-like factor 2* was found to be more common among Hispanics and is associated with poor outcome in pediatric B-progenitor ALL.[27] A component of genomic variation that co-segregated with Native American ancestry was associated with risk of ALL relapse.[28] However, adjusting for some biological differences, inequalities between the racial/ethnic minorities and NH-Whites were still observed.[7] Access and adherence to the treatment are also likely explanations for the inequalities. Lund *et al.* reported that NH-Blacks and Hispanics were less likely to enroll into clinical trials, [29] and Bhatia *et al.* demonstrated that those who did participate were less likely to adhere to the treatment.[30, 31]

Several limitations of this study are pertinent in interpreting its results. First, possibilities in the misclassification of race/ethnicity should be considered. SEER racial/ethnic classifications were reported to have an excellent agreement with self-reported racial classifications, except for the AIAN classification: the 5-year overall survival for AIAN cancer patients based on SEER race classifications was reported to be much lower than that for self-identified AIAN cancer

patients.[32] The increase in the proportion of multi-racial and multi-ethnic children has been reported in the US over time.[33] Although cancer registries include up to five race fields for each patients since 2000, only the primary race information is available in the SEER dataset. Moreover, it is unclear whether the information captured in these fields is reflective of multi-race status or different race coding reported by different facilities for a given patient. SEER race coding algorithms preferentially codes the minority (non-White) race in the primary race field. Nonetheless, given the increase in prevalence of multi-race/ethnicity children in the US, it would be worthwhile to examine survival patterns for the growing population of young multi-race/ethnicity cancer patients in datasets in which this information is explicitly captured. Second, survival of more recently diagnosed cases in 2000-10 was estimated with a relatively shorter follow-up time. Third, causes of death might have been misclassified in determining ALL mortality. The SEER cause-specific death classification is defined based on cause of deaths in conjunction with the tumor sequence, site of the original cancer diagnosis; and comorbidities, aiming to capture deaths that are related to the specific cancer but are not coded as such.[17] To supplement this limitation, death due to all causes was analyzed as the secondary outcome, and similar results were found and presented in the supplementary materials. However, some other important endpoints, such as the event-free survival, cannot be estimated as treatment failure information (e.g. relapse or refractory disease) is not captured by SEER data. Moreover, the lack of information regarding clinical presentation (e.g., WBC counts), tumor biology, and treatment of ALL cases in cancer registries limits the interpretation of the inequalities and their trends. Lastly, the inequalities and their trends found on the SEER 9 registries may not be fully applicable to other SEER registries and to other geographic locations outside of the SEER program.

In conclusion, survival inequalities changed differently across subgroups of children with ALL. Underlying causes of the differential trends need to be examined, such that targeted interventions can be developed to reduce growing or persistent inequalities among Hispanics and AIANs, as well as among APIs boys, APIs and NH-Blacks diagnosed at 1-9 years old.

Table 3-1. Characteristics of Children Diagnosed with Acute Lymphoblastic Leukemia by Race/Ethnicity, SEER 9 Registries, 1975-2010

	All Children	NH-White	NH-Black	Hispanic	API	AIAN	
	No. (%)						P-value
All Cases	7365 (100.0)	5000 (67.9)	532 (7.2)	1096 (14.9)	626 (8.5)	111 (1.5)	
Sex							0.639
Girls	3183 (43.2)	2179 (43.6)	237 (44.5)	460 (42.0)	264 (42.2)	43 (38.7)	
Boys	4182 (56.8)	2821 (56.4)	295 (55.5)	636 (58.0)	362 (57.8)	68 (61.3)	
Age at Diagnosis							0.002
<1	240 (3.3)	154 (3.1)	23 (4.3)	43 (3.9)	19 (3.0)	1 (0.9)	
01-09	5231 (71.0)	3558 (71.2)	345 (64.9)	766 (69.9)	480 (76.7)	82 (73.9)	
10-19	1894 (25.7)	1288 (25.7)	164 (30.8)	287 (26.2)	127 (20.3)	28 (25.2)	
Diagnosis Period							<0.001
1975-1983	1468 (19.9)	1140 (22.8)	93 (17.5)	129 (11.8)	90 (14.4)	16 (14.4)	
1984-1991	1591 (21.6)	1133 (22.7)	115 (21.6)	174 (15.9)	137 (21.9)	32 (28.8)	
1992-1999	1691 (23.0)	1155 (23.1)	138 (25.9)	228 (20.8)	147 (23.5)	23 (20.7)	
2000-2010	2615 (35.5)	1572 (31.4)	186 (35.0)	565 (51.6)	252 (40.3)	40 (36.0)	

Abbreviation: NH-White, non-Hispanic -White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.

Table 3-2. Cumulative Acute Lymphoblastic Leukemia (ALL) Mortality among 7365 Children Diagnosed with ALL by Diagnosis Period, SEER 9 Registries, 1975-2010

	1975-1983	1984-1991	1992-1999	2000-2010
		5-year Cumulative ALL Mortality (95% CI)		
All children	0.35 (0.32, 0.37)	0.23 (0.21, 0.26)	0.16 (0.14, 0.17)	0.10 (0.09, 0.11)
Race/Ethnicity				
NH-White	0.33 (0.30, 0.36)	0.20 (0.18, 0.23)	0.13 (0.11, 0.15)	0.08 (0.07, 0.10)
NH-Black	0.48 (0.38, 0.58)	0.43 (0.33, 0.51)	0.22 (0.15, 0.29)	0.11 (0.06, 0.16)
Hispanic	0.43 (0.34, 0.51)	0.30 (0.23, 0.37)	0.22 (0.17, 0.28)	0.15 (0.12, 0.19)
API	0.31 (0.22, 0.41)	0.20 (0.14, 0.27)	0.15 (0.10, 0.21)	0.10 (0.07, 0.15)
AIAN	0.38 (0.15, 0.61)	0.41 (0.23, 0.57)	0.26 (0.10, 0.45)	0.19 (0.08, 0.32)
Sex				
Girls	0.30 (0.26, 0.33)	0.21 (0.18, 0.24)	0.13 (0.10, 0.15)	0.09 (0.07, 0.11)
Boys	0.39 (0.35, 0.42)	0.26 (0.23, 0.29)	0.18 (0.15, 0.20)	0.11 (0.10, 0.13)
Age at Diagnosis				
<1	0.68 (0.53, 0.79)	0.63 (0.50, 0.74)	0.37 (0.23, 0.52)	0.31 (0.21, 0.41)
1-9	0.26 (0.24, 0.29)	0.15 (0.13, 0.18)	0.10 (0.09, 0.12)	0.05 (0.04, 0.07)
10-19	0.51 (0.47, 0.56)	0.42 (0.37, 0.47)	0.29 (0.25, 0.33)	0.20 (0.17, 0.23)

Abbreviation: 95% CI, 95% confidence interval; NH-White, non-Hispanic -White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.

Table 3-3. Hazard Ratios of Acute Lymphoblastic Leukemia Mortality among Racial/Ethnic Groups (Compared to Non-Hispanic Whites), by Diagnosis Period, SEER 9 Registries, 1975-2010

	1975-1983	1984-1991	1992-1999	2000-2010	
	[a]Adjusted HR (95%CI)				[b]Trend P-value
Race/Ethnicity					
NH-White	1.00	1.00	1.00	1.00	
NH-Black	1.46 (1.09, 1.94)	2.09 (1.57, 2.79)	1.62 (1.13, 2.32)	1.21 (0.74, 1.96)	0.655
Hispanic	1.28 (0.98, 1.66)	1.58 (1.21, 2.07)	1.66 (1.23, 2.25)	1.95 (1.48, 2.58)	0.023
API	1.05 (0.76, 1.46)	1.11 (0.77, 1.59)	1.22 (0.81, 1.85)	1.37 (0.91, 2.08)	0.275
AIAN	1.26 (0.60, 2.65)	2.19 (1.28, 3.75)	2.10 (0.93, 4.75)	2.28 (1.11, 4.67)	0.279
Age at Diagnosis					
Age <1 year old	3.60 (2.57, 5.05)	6.01 (4.29, 8.41)	4.22 (2.52, 7.09)	7.57 (4.85, 11.80)	0.028
Age 1-9 years old	1.00	1.00	1.00	1.00	
Age 10-19 years old	2.04 (1.73, 2.41)	2.67 (2.20, 3.24)	2.68 (2.12, 3.39)	4.01 (3.09, 5.19)	<0.001
Sex					
Girls	1.00	1.00	1.00	1.00	
Boys	1.35 (1.15, 1.59)	1.25 (1.04, 1.52)	1.40 (1.11, 1.78)	1.32 (1.02, 1.70)	0.999

Abbreviation: 95% CI, 95% confidence interval; NH-White, non-Hispanic -White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.
[a]Hazard ratios (HR) adjusted for all other factors shown in the table.
[b] Tests of a linear trend in the change of inequalities with respect to a variable (e.g., race/ethnicity) over time were performed by treating the four-category diagnosis period variable as continous in the interaction term of the diagnosis period and the variable in the Cox regression models.

Table 3-4. Trends in Hazard Ratios for Acute Lymphoblastic Leukemia Mortality among Racial/Ethnic Groups (Compared to non-Hispanic Whites) by Age and by Sex, SEER 9 Registries, 1975-2010

	1975-1983	1984-1991	1992-1999	2000-2010	
	[a]Adjusted HR (95%CI)				[b]Trend P-value
Aged <1 year					
NH-Black	0.50 (0.12, 2.17)	1.32 (0.46, 3.77)	1.97 (0.54, 7.16)	1.42 (0.39, 5.11)	0.308
Hispanic	1.80 (0.66, 4.89)	1.57 (0.69, 3.58)	0.50 (0.11, 2.30)	1.76 (0.69, 4.49)	0.745
API	0.51 (0.16, 1.69)	--	0.85 (0.11, 6.65)	0.69 (0.15, 3.09)	0.705
AIAN	--	--	--	37.68 (4.03, 352.65)	--
Aged 1-9 years					
NH-Black	1.81 (1.21, 2.69)	2.63 (1.77, 3.89)	2.09 (1.27, 3.42)	1.90 (0.93, 3.89)	0.805
Hispanic	1.42 (1.00, 2.01)	1.62 (1.11, 2.35)	1.81 (1.20, 2.73)	2.12 (1.33, 3.38)	0.143
API	1.23 (0.83, 1.85)	1.19 (0.77, 1.82)	1.47 (0.89, 2.44)	2.02 (1.10, 3.69)	0.175
AIAN	1.01 (0.38, 2.71)	2.06 (1.01, 4.19)	1.87 (0.69, 5.09)	0.94 (0.13, 6.84)	0.696
Aged 10-19 years					
NH-Black	1.47 (0.95, 2.27)	1.74 (1.09, 2.77)	1.19 (0.68, 2.11)	0.77 (0.36, 1.68)	0.151
Hispanic	1.02 (0.66, 1.60)	1.57 (1.02, 2.42)	1.74 (1.09, 2.77)	1.87 (1.28, 2.71)	0.043
API	0.93 (0.51, 1.72)	1.14 (0.58, 2.24)	0.95 (0.44, 2.05)	1.16 (0.61, 2.18)	0.683
AIAN	1.72 (0.55, 5.39)	2.42 (1.07, 5.52)	3.02 (0.74, 12.33)	2.42 (1.05, 5.58)	0.633
Girls					
NH-Black	1.71 (1.09, 2.69)	2.23 (1.45, 3.44)	1.55 (0.87, 2.76)	1.32 (0.56, 3.09)	0.509
Hispanic	1.63 (1.12, 2.38)	1.69 (1.09, 2.62)	1.09 (0.61, 1.93)	3.01 (1.96, 4.64)	0.082
API	0.71 (0.39, 1.32)	1.17 (0.64, 2.12)	1.03 (0.50, 2.15)	0.93 (0.40, 2.19)	0.586
AIAN	1.42 (0.45, 4.45)	1.89 (0.70, 5.14)	3.12 (0.97, 10.00)	3.25 (0.79, 13.44)	0.256
Boys					
NH-Black	1.42 (0.98, 2.07)	1.97 (1.34, 2.91)	1.67 (1.06, 2.65)	1.13 (0.63, 2.04)	0.771
Hispanic	1.04 (0.71, 1.51)	1.54 (1.10, 2.15)	2.01 (1.40, 2.87)	1.43 (0.99, 2.08)	0.101
API	1.27 (0.87, 1.86)	1.10 (0.70, 1.72)	1.36 (0.83, 2.24)	1.61 (1.00, 2.60)	0.356
AIAN	1.10 (0.41, 2.94)	2.31 (1.22, 4.38)	1.57 (050, 4.93)	1.94 (0.84, 4.44)	0.503

Abbreviation: HR, hazard ratio; 95% CI, 95% confidence interval; NH-White, non-Hispanic -White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.
[a]Hazard ratios (HR) adjusted for all other factors shown in the table.
[b]Tests of a linear trend in the change of racial/ethnic inequalities over time were performed by treating the four-category diagnosis period variable as continous in the interaction term of the diagnosis period and race/ethnicity in the Cox regression models.
"-- ": Not estimatable due to limited number of cases.

Supplementary Table 3-1. Overall Survival Probabilities among 7365 Children Diagnosed with Acute Lymphoblastic Leukemia by Diagnosis Period, SEER 9 Registries, 1975-2010

	1975-1983	1984-1991	1992-1999	2000-2010
		5-year Overall Survival (95% CI)		
All children	0.61 (0.58, 0.63)	0.74 (0.72, 0.76)	0.83 (0.81, 0.84)	0.88 (0.87, 0.89)
Race/Ethnicity				
NH-White	0.62 (0.60, 0.65)	0.77 (0.75, 0.80)	0.85 (0.83, 0.87)	0.91 (0.89, 0.92)
NH-Black	0.46 (0.36, 0.56)	0.57 (0.47, 0.65)	0.75 (0.67, 0.82)	0.87 (0.80, 0.91)
Hispanic	0.55 (0.46, 0.64)	0.66 (0.58, 0.72)	0.74 (0.68, 0.79)	0.83 (0.79, 0.86)
API	0.63 (0.53, 0.72)	0.75 (0.67, 0.82)	0.84 (0.76, 0.89)	0.87 (0.82, 0.91)
AIAN	0.56 (0.30, 0.76)	0.56 (0.38, 0.71)	0.74 (0.51, 0.87)	0.79 (0.62, 0.89)
Sex				
Girls	0.66 (0.62, 0.69)	0.76 (0.73, 0.79)	0.86 (0.83, 0.88)	0.89 (0.87, 0.91)
Boys	0.57 (0.53, 0.60)	0.72 (0.69, 0.75)	0.80 (0.78, 0.83)	0.87 (0.85, 0.89)
Age at Diagnosis				
<1	0.28 (0.17, 0.41)	0.35 (0.23, 0.47)	0.56 (0.40, 0.69)	0.63 (0.51, 0.72)
1-9	0.70 (0.67, 0.73)	0.82 (0.79, 0.74)	0.88 (0.86, 0.90)	0.94 (0.93, 0.95)
10-19	0.43 (0.38, 0.47)	0.57 (0.51, 0.61)	0.69 (0.64, 0.73)	0.77 (0.73, 0.80)

Abbreviation: 95% CI, 95% confidence interval; NH-White, non-Hispanic -White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.

Supplementary Table 3-2. Hazard Ratios of All-cause Mortality among Racial/Ethnic Groups (Compared to Non-Hispanic Whites), by Diagnosis Period, SEER 9 Registries, 1975-2010

	1975-1983	1984-1991	1992-1999	2000-2010	
	[a]Adjusted HR (95%CI)				[b]Trend P-value
Race/Ethnicity					
NH-White	1.00	1.00	1.00	1.00	
NH-Black	1.52 (1.17, 1.97)	1.90 (1.44, 2.50)	1.74 (1.25, 2.41)	1.36 (0.89, 2.08)	0.875
Hispanic	1.18 (0.92, 1.52)	1.53 (1.20, 1.96)	1.82 (1.38, 2.39)	1.89 (1.45, 2.45)	0.005
API	1.18 (0.89, 1.57)	1.26 (0.92, 1.71)	1.22 (0.83, 1.79)	1.48 (1.02, 2.15)	0.371
AIAN	1.21 (0.60, 2.44)	1.94 (1.16, 3.26)	1.81 (0.80, 4.08)	2.19 (1.12, 4.30)	0.256
Age at Diagnosis					
Age <1 year old	3.37 (2.45, 4.64)	5.03 (3.63, 6.98)	4.35 (2.74, 6.92)	7.91 (5.26, 11.89)	0.005
Age 1-9 years old	1.00	1.00	1.00	1.00	
Age 10-19 years old	2.04 (1.75, 2.38)	2.43 (2.03, 2.91)	2.54 (2.04, 3.15)	4.26 (3.35, 5.42)	<0.001
Sex					
Girls	1.00	1.00	1.00	1.00	
Boys	1.33 (1.15, 1.55)	1.24 (1.04, 1.48)	1.44 (1.15, 1.79)	1.28 (1.02, 1.62)	0.951

Abbreviation: HR, hazard ratio; 95% CI, 95% confidence interval; NH-White, non-Hispanic white; NH-Black, non-Hispanic black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.
[a]Hazard ratios (HR) adjusted for all other factors shown in the table.
[b] Tests of a linear trend in the change of inequalities with respect to a variable (e.g., race/ethnicity) over time were performed by treating the four-category diagnosis period variable as continous in the interaction term of the diagnosis period and the variable in the Cox regression models.

Supplementary Table 3-3. Hazard Ratios of Acute Lymphoblastic Leukemia Mortality in Hispanics Compared to Non-Hispanic Whites, by Diagnosis Period and SEER Registry

	1975-1983	1984-1991	1992-1999	2000-2010	
	[a]Adjusted HR (95%CI)				[b]Trend P-value
SEER Registry					
Atlanta	--	0.68 (0.15, 3.05)	1.11 (0.25, 4.90)	4.88 (2.05, 11.61)	0.005
Connecticut	1.10 (0.50, 2.39)	1.90 (0.99, 3.64)	1.22 (0.40, 3.79)	1.46 (0.58, 3.67)	0.757
Detroit	4.04 (1.61, 10.14)	1.61 (0.55, 4.67)	5.99 (1.77, 20.26)	1.76 (0.51, 6.06)	0.793
Hawaii	3.89 (0.96, 15.77)	54.11 (4.58, 638.89)	--	--	0.081
Iowa	--	--	--	0.36 (0.38, 4.83)	--
New Mexico	1.35 (0.76, 2.38)	1.91 (0.94, 3.86)	0.95 (0.46, 1.92)	1.31 (0.59, 2.91)	0.650
San Francisco	0.64 (0.30, 1.38)	1.58 (0.87, 2.88)	1.62 (0.81, 3.23)	2.91 (1.23, 6.91)	0.014
Seattle	2.63 (0.81, 8.53)	0.70 (0.10, 5.11)	2.12 (0.74 (6.06)	1.18 (0.49, 2.87)	0.491
Utah	0.92 (0.36, 2.37)	1.03 (0.30, 3.48)	1.68 (0.63, 4.46)	2.93 (1.23, 6.99)	0.068

Abbreviation: HR, hazard ratio; 95% CI, 95% confidence interval;
[a] Adjusted for age at diagnosis and sex.
[b] Tests of a linear trend in the change of inequalities with respect to race/ethnicity over time were performed by treating the four-category diagnosis period variable as continous in the interaction term of the diagnosis period and race/ethnicity in the Cox regression models.
"-- ": Not estimatable due to limited number of cases

Supplementary Table 3-4. Relative Proportion of Hispanic population in Each SEER Registry by Diagnosis Period

	1975-1983	1984-1991	1992-1999	2000-2010
SEER Registry	%			
Atlanta	1.16	6.56	7.43	24.47
Connecticut	6.70	13.33	13.51	18.57
Detroit	2.72	2.81	2.45	5.90
Hawaii	5.13	2.38	3.53	3.85
Iowa	1.30	1.60	3.98	8.59
New Mexico	54.81	44.80	47.66	53.97
San Francisco	14.05	23.11	28.57	37.20
Seattle	2.86	3.14	6.50	14.32
Utah	8.33	5.95	13.50	20.55

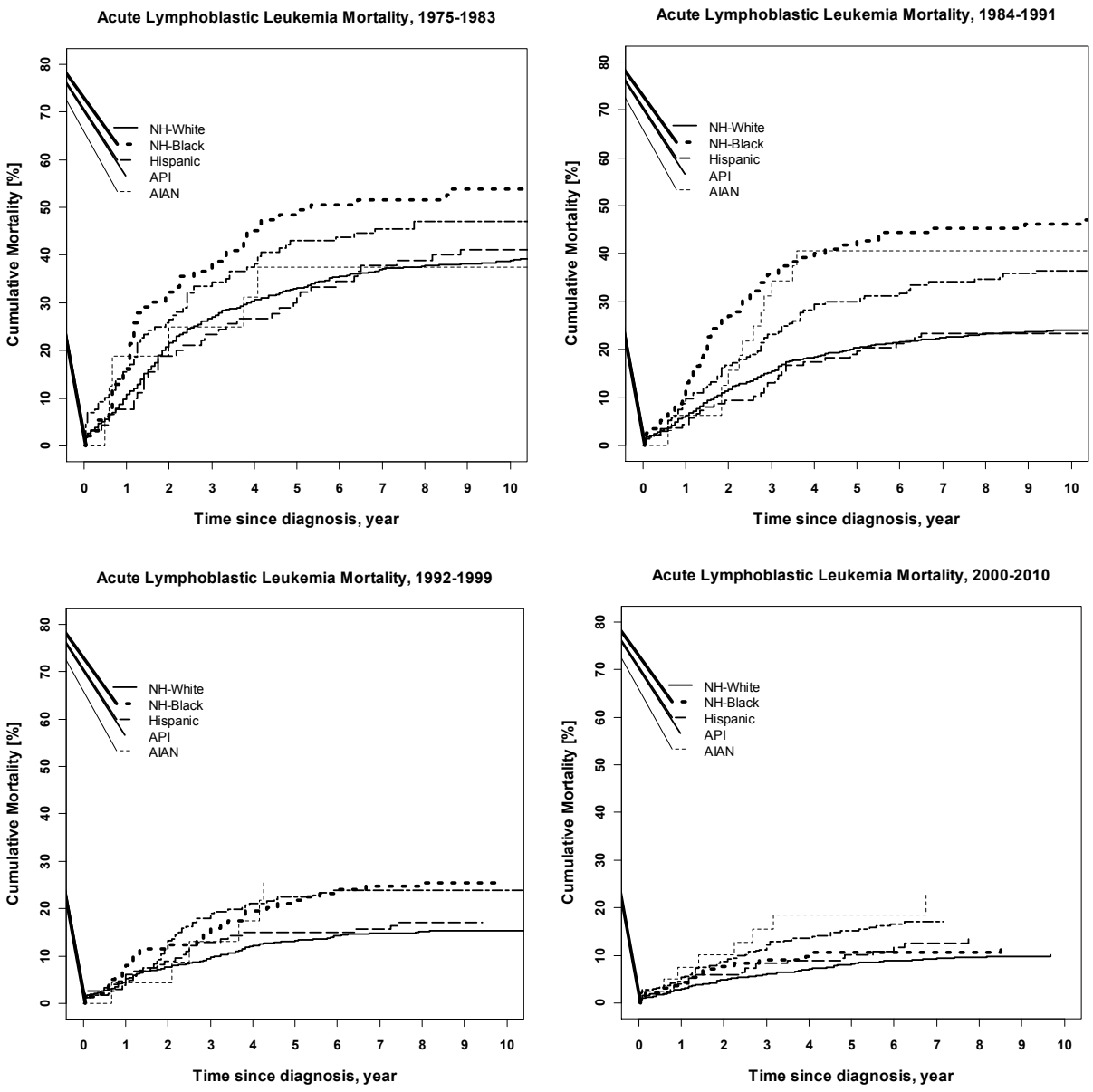

Figure 3-1. Cumulative Mortality due to Acute Lymphoblastic Leukemia, by Diagnosis Period and Race/Ethnicity, SEER 9 Registries, 1975-2010

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CHAPTER 4: CONCLUSIONS

4.1 OVERALL SUMMARY

Inequalities in the occurrence and outcomes of health conditions, especially those by race/ethnicity and SEP, have been widely investigated. Quantifying, understanding, improving the health inequalities, and monitoring the trend of the inequalities over time are important research focuses. In this thesis research, our objectives were to investigate several questions related to the inequalities in incidence and survival of childhood ALL by race/ethnicity and SEP, with the goal to quantify and understand the inequalities, and monitor the trend. This population-based investigation well documented the inequalities with minimal selection bias, which often presented in studies based on cooperative clinical trials or single institutions caused by variation in access to care, and in case-control studies caused by case/control selection. The SEER cancer registries which have been collecting population-based cancer incidence and survival data since 1973 also provided the opportunity to quantify the longitudinal trend of the inequalities.

In Chapter 2, we quantified the incidence of childhood ALL by SEP, age, and sex, in each racial and ethnic group in the United States. We found risk of childhood ALL was positively associated with census tract-level SEP in NH-Whites, NH-Blacks, APIs and AIANs, but negatively associated with SEP in Hispanics, which had never been reported before. In Chapter 3, we presented a comprehensive examination of inequality trends in survival among US children with ALL by race/ethnicity, age at diagnosis and sex over 3.5 decades. We found racial and ethnic inequalities in mortality due to ALL diminished over time for NH-Blacks, which was consistent with previous studies, but worsened significantly for Hispanics and non-significantly for APIs and AIANs.

4.2 LIMITATIONS

Limitations of this research include those that arise from the nature of the SEER cancer registry data we utilized. Important clinical and therapeutic details of childhood ALL are not available in SEER data; we were not able to adjust for and investigate those factors that might explain some observed inequalities. Studies from cooperative group clinical trials or single institutions usually collect details regarding the disease characteristics and therapeutic exposures, thus play key roles in understanding the inequalities. In addition, SEP information is very limited in most US public health surveillance databases.[1, 2] In SEER cancer registries, individual-level SEP data are not available and census tract-level SEP data are not publically available due to concerns about confidentiality. Most previous population-based studies used county-level SEP measures. The composite SEP index which was developed and made available in SEER upon request in 2014 provided the opportunity to analyze the association between census tract-level SEP and risk of childhood ALL.[3] This is a more precise representation of SEP because census tracts are much smaller than counties and more homogeneous in residence socioeconomic characteristics. However, we were unable to examine the potentially distinct association of each single SEP dimension with risk of childhood ALL.

4.3 IMPLICATIONS

The ultimate goal, as stated in *Healthy People 2020*, is to achieve health equity, eliminate disparities, and improve the health of all groups.[4] "Achieving health equity requires valuing everyone equally with focused and ongoing societal efforts to address avoidable inequalities, historical and contemporary injustices, and the elimination of health and health care disparities".[4]

Efforts to reduce the risk of childhood ALL for all groups are limited, as the etiology of ALL is unclear. In fact, there has been a gradual increase in the incidence of childhood ALL over time.[6] Researchers continue to study potential causal factors. Studies on association between SEP and risk of childhood ALL have led to speculations about a range of potential etiological factors linked with SEP, among which infection-based hypotheses hold the strongest evidence.[7, 8] The findings from this thesis research are consistent with the notion that infection is a strong candidate of causal factors for childhood ALL, and also imply potential ethnic difference in etiology of childhood ALL.

Efforts have been successful in improving the survival after childhood ALL for all groups, considering the dramatic absolute increase in survival probabilities among children of different races/ethnicities, diagnosis ages, and sex. However, health equity has not been achieved yet. This thesis research shows evidence from population-based cancer registry data and informs health care practitioners and health policy makers regarding the burden of health inequalities and the progress of inequalities in survival among US children with ALL.

Inequalities measured in absolute terms and relative terms have different implications. The absolute measures do not depend on the baseline level of the variable, quantify the absolute size of the differences, reflect the burden of inequalities in the population, and thus provide useful epidemiological input into decision making. For example, efforts toward treatment improvement among infants and older children with ALL will likely increase overall survival more than efforts toward improving the sex difference, as the significant relative inequality in sex corresponds to a

small absolute difference only. Measuring health inequalities using relative terms is useful for monitoring impacts of policies that target improvement of health outcomes among the disadvantaged/worse off to achieve health equity.[9] Reduction in an absolute measure of inequality can occur without any corresponding reduction in the relative measure, but narrowing in a relative measure of health inequality necessarily leads to decrease in the absolute inequality. For example, it is encouraging that survival after childhood ALL improved significantly for children of all race/ethnicity; however, in order to achieve health equity, efforts are needed to further understand the inequalities among racial and ethnic minorities so that targeted interventions can be developed to help minorities catch up with NH-Whites in survival after ALL.

4.4 FUTURE RESEARCH

More research is needed to investigate the association between SEP, race/ethnicity and risk of childhood ALL. It would be useful to investigate the association of different SEP measures separately other than the composite SEP index with risk of childhood ALL to test the hypothesis that different SEP measures represent different risk factors. Data on single census tract-level SEP measures are available by accessing data through specific SEER registries. This thesis research also showed necessities of considering potential ethnic differences (Hispanics vs. non-Hispanics) in etiological research of childhood ALL.

Future research on racial and ethnic inequalities in survival after childhood ALL should further investigate the underlying reasons of persistent inequalities observed among children of specific race/ethnicity groups and of certain age and sex. Also of interest is to examine the prognosis of

ALL among recent Hispanic immigrants. Studies to investigate the SEP inequalities in survival among US children with ALL can also be conducted utilizing the available composite SEP index data. Moreover, evaluation of how race/ethnicity and SEP interact together in influencing the survival after childhood ALL may provide better understanding of the inequalities by race/ethnicity and SEP. In fact, this thesis research has investigated the differential associations of SEP by race/ethnicity with survival after childhood ALL in a preliminary fashion, which has not been examined fully previously. Since the work was preliminary, its findings are attached as appendix of this thesis. Briefly, statistically significant SEP gradient was observed among NH-Whites and APIs in survival, with higher mortality hazard among children of lower SEP. However, no SEP gradient in survival was found among NH-Blacks, Hispanics and AIANs.

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APPENDIX: PRELIMINARY FINDINGS ON DIFFERENTIAL SOCIOECONOMIC INEQUALITIES IN SURVIVAL OF CHILHOOD ACUTE LYMPHOBLASTIC LEUKEMIA BY RACE/ETHNICITY

Appendix Table 1. Overall Survival Probabilities among 8377 Children Diagnosed with Acute Lymphoblastic Leukemia by Race/Ethnicity and SEP, SEER 16 Registries[a], 2000-2010

	[b]All Children	NH-White	NH-Black	Hispanic	API	AIAN
			[c]Five-Year Survival Probability (95% CI)			
All Cases	0.85 (0.64, 0.86)	0.89 (0.88, 0.90)	0.81 (0.77, 0.85)	0.81 (0.80, 0.83)	0.86 (0.83, 0.89)	0.77 (0.63, 0.86)
[d]SEP						
Lowest	0.81 (0.79, 0.83)	0.85 (0.81 - 0.89)	0.81 (0.74 - 0.87)	0.80 (0.77 - 0.82)	0.82 (0.68 - 0.90)	0.76 (0.48 - 0.90)
Low	0.84 (0.82, 0.86)	0.86 (0.82 - 0.88)	0.88 (0.80 - 0.93)	0.83 (0.80 - 0.86)	0.77 (0.62 - 0.87)	0.72 (0.44 - 0.87)
Median	0.86 (0.84, 0.88)	0.89 (0.86 - 0.91)	0.74 (0.63 - 0.83)	0.84 (0.80 - 0.87)	0.84 (0.75 - 0.90)	0.69 (0.21 - 0.91)
High	0.87 (0.85, 0.89)	0.90 (0.87 - 0.92)	0.84 (0.72 - 0.91)	0.80 (0.75 - 0.85)	0.87 (0.79 - 0.92)	0.67 (0.05 - 0.95)
Highest	0.89 (0.88, 0.91)	0.91 (0.89 - 0.93)	0.75 (0.56 - 0.87)	0.81 (0.74 - 0.87)	0.91 (0.85 - 0.94)	--

Abbreviation: SEP, socioeconomic position; 95% CI, 95% confidence interval; NH-White, non-Hispanic -White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.
[a]Cases from the Alaska Native Tumor Registry and the Louisiana Tumor registry were excluded due to the unavailability of SEP data.
[b]Children aged 0 to 19 years who were diagnosed with a first primary malignant acute lymphoblastic leukemia during 2000-2010 in the SEER program.
[c]Kaplan-Meier method was used to estimate the overall five-year survvial probabilities by race/ethnicity and SEP.
[d]SEP was assessed using a census tract-level composite SEP index developed by SEER using factor analysis on the seven SEP measures identified by Yost *et al.*
"-- ": Not estimatable due to limited number of cases.

Appendix Table 2. Adjusted Hazard Ratios of Acute Lymphoblastic Leukemia Mortality by Race/Ethnicity and SEP (Compared to NH-Whites with the Highest SEP), SEER 16 Registries[a], 2000-2010

	NH-White	NH-Black	Hispanic	API	AIAN
	[b]Adjusted Hazard Ratios(95% CI)				
[c]**SEP**					
Highest	1.00	2.89 (1.40 - 5.96)	2.13 (1.41 - 3.24)	0.92 (0.54 - 1.55)	--
High	0.99 (0.72 - 1.37)	1.55 (0.77 - 3.16)	2.41 (1.72 - 3.37)	1.46 (0.83 - 2.55)	2.21 (0.46 - 10.65)
Median	1.21 (0.87 - 1.68)	2.58 (1.55 - 4.28)	1.93 (1.41 - 2.64)	2.25 (1.28 - 3.97)	3.37 (1.30 - 8.79)
Low	1.61 (1.18 - 2.20)	0.92 (0.48 - 1.76)	1.87 (1.41 - 2.47)	1.72 (0.84 - 3.53)	3.54 (1.63 - 7.72)
Lowest	1.68 (1.18 - 2.38)	1.85 (1.19 - 2.87)	2.23 (1.73 - 2.89)	2.02 (0.99 - 4.13)	1.98 (0.65 - 6.05)
Trend test	<0.001	0.386	0.907	0.014	0.217

Abbreviation: SEP, socioeconomic position; 95% CI, 95% confidence interval; NH-White, non-Hispanic -White; NH-Black, non-Hispanic-Black; API, Asian/Pacific Islander; AIAN, American Indian/Alaska Native.
[a]Cases from the Alaska Native Tumor Registry and the Louisiana Tumor registry were excluded due to the unavailability of SEP data.
[b]Multivariable Cox regression analyses were used to estimate the hazard ratios and their 95% CI for comparisons of mortality due to acute lymphoblastic leukemia across race/ethnicity groups and SEP levels, adjusting for age at diagnosis and sex.
[c]SEP was assessed using a census tract-level composite SEP index developed by SEER using factor analysis on the seven SEP measures identified by Yost *et al.*
"-- ": Not estimatable due to limited number of cases.