CHILDHOOD CANCER DISPARITIES IN TEXAS

by

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LIST OF ABBREVIATIONS

Abbreviation	Description
AA	African-Americans
ACS	American Cancer Society
CHS	Center for Health services
COG	Children Oncology Group
E2SFCA	Enhanced 2 Step Floating Catchment Area
FCA	Floating Catchment Area
HIS	Hispanics
IRB	Institutional Review Board
NHW	Non-Hispanic White
SES	Socioeconomic Status
SPAI	Spatial Access Index
TDSHS	Texas Department of State Health Services
TCR	Texas Cancer Registry

ABSTRACT

Cancer is a major public health concern and second leading cause of death in the United States. Although cancer in children represents less than 1% of all new cancer diagnoses, it accounts for considerable death and decreases the span of life. Childhood cancer incidence rate has slowly increased by 0.6 % each year since 1975. Fortunately, there has been a significant improvement in childhood cancer survival because of advancement in medical science and successful enrollment in the clinical trial. However, neither all people receive benefit from such progress, nor all people receive equal benefits. Different population groups of cancer patients experience varying degrees of burden based on the cancer control continuum which includes cancer etiology, prevention, detection, diagnosis, treatment, and overall survivorship.

The study investigated childhood cancer disparities in the state of Texas based on data from 1995 to 2014 from the perspective of race/ethnicity, geographic location, and other social domains. This dissertation research used population weighted risk difference to measure the geographic variation of racial/ethnic disparities of childhood cancer late-stage diagnosis. Enhanced 2-step floating catchment area (E2SFCA) method was used to calculate the relative spatial access to the Children Oncology Group (COG) hospitals. Geographic variation of childhood cancer stage at diagnosis was measured using spatial scan statistics.

Multilevel logistic regression was used to analyze how individual and contextual level factors impact the occurrence of childhood cancer disparity by race/ethnicity,

socioeconomic status (SES), socio-cultural factor, education, percent African-Americans, spatial access to COGs and rural-urban commuting area and percent health insurance coverage. In addition, this study used newly developed causal mediation analysis method to examine childhood cancer survival. The study investigated the effect of race/ethnicity on overall survival of childhood cancer patients while mediated through socioeconomic status and spatial accessibility mediators.

There were 54 % of the cases diagnosed in their late stage from the study cohort. Although there were few African-American cases compared with non-Hispanic white and Hispanics, they showed significant geographic variation in racial/ethnic disparities compared with their non-Hispanic white counterpart. The study revealed that Hispanic children were more likely to be diagnosed at late-stage after adjusting for age, race/ethnicity, SES, socio-culture, education, spatial access to COGs, percentage of African-American and health insurance coverage. The study also identified a significant difference in spatial accessibility to COG hospitals based on rural-urban commuting area. Moreover, the study found that contextual-level factors explained part of the childhood cancer disparities.

Considering all cancer site groups, African-American had statistically significant higher hazard of death compared with non-Hispanic whites mediated by socio-economic status and spatial accessibility. Survival analysis indicated that non-Hispanic white had significantly higher survival probabilities compared with African-Americans. However,

the study did not find a significant difference in the survival of Hispanics and Non-Hispanic whites.

Results from this study will contribute to developing effective childhood cancer intervention programs in the targeted socially underprivileged areas with lower-socioeconomic status, limited English-speaking household, lower education-level, and areas with a higher percentage of African-Americans. Furthermore, the finding of this study will contribute to the geographical resource allocation system which in turn help to facilitate preventive health care service and alleviate the diseases burden in children.

1. INTRODUCTION

1.1 Background

Cancer is the leading cause of death and poses a significant burden on both economically more and less developed countries worldwide (Torre et al. 2015). In 2012, an estimated 14.1 million new cancer cases and people died of cancer 8.2 million around the globe (Stewart, Wild, and International Agency for Research on Cancer 2014). The second most common reason for death in the US is cancer that surpassed just by coronary illness, records for about 1 of every 4 deaths (American Cancer Society 2015). Though cancer is not the most common in childhood, it accounts for considerable death in children, decreases the span of life. Although children and adolescents cancer incidence rates stabilized over the past five data years, it has been increasing slightly by 0.6% per year since 1975 (Siegel, Miller, and Jemal 2018). Siegel, Miller, and Jemal (2018) also reported that in the year 2018 an estimated 10,590 new cases were expected to occur among children 0 to 14 years and 1,180 will die from the diseases.

Fortunately, there has been a significant improvement in the increase of survival and decrease of cancer mortality. In the United States, overall five-year survival rate now surpasses 80% for children with cancer, and almost 75% of them will live 10 years following of their diagnosis (Armenian et al. 2013). However, neither all people receive benefit from such progress, nor all people receive equal benefits. Health disparity exists among different population groups of cancer patients based on the cancer control continuum which includes cancer etiology, prevention, detection, diagnosis, treatment, and overall survivorship (Figure1.1).

Health disparity discussed in the name of two other terms called “health inequalities” and “health inequity” in and outside the US. The concept of equity in health care helps to understand the health disparity and its related terms. According to Whitehead et al. (1992) “Equity in health care is defined as equal access to available care for equal need, equal utilization for equal need and equal quality of care for all.” In another way health disparity should be observed as a chain of occasions connoted by a distinction in (1) individual living environment (2) the quality of health care, utilization, and access to (3) individual health condition, or (4) merit examination of health outcomes (Carter-Pokras and Baquet 2002). Race/ethnicity and socioeconomic status (SES) burdens disparity in adults with cancers (Freeman 1989) as well as children. Identifying the vulnerable population is still a major challenge in health disparity research.

Cancer treatment and its likelihood of cure marked significantly in the past decades because of the sophisticated diagnostic procedure and continuous improvisation of multimodal treatment strategies. However, childhood cancer and its treatment have remained a challenge not only for public health viewpoint but also for patients, their families, and doctors taking care of them (Kaatsch 2010). Developed nations such as Switzerland where health insurance is mandatory and provide high-quality healthcare, childhood cancer survival still vary depending on the socioeconomic status of the family (Adam et al. 2016). This scenario is much worse in developing nations, for instance, India where socioeconomic differences are believed to be responsible for geographic variation in childhood cancer mortality (Gupta et al. 2016). Though there is an improvement in the overall health of people in the US, a disproportionate burden of illness and premature death prevails in racial/ethnic minorities and other population

group (National Institutes of Health 2009). The US Department of Health and Human Services announced four overarching goals with the banner of '*Healthy People 2020*' to achieve. The second goal emphasizes the importance of (a) achieving health equity, (b) eliminate health disparities (US Department of Health and Human Services 2008).

We have made little progress in decreasing disparities at the population level regardless of expanded thoughtfulness to health disparities (Gehlert and Colditz 2011). This project examined childhood cancer disparities in Texas based on data from 1995 to 2014 from the perspective of geographic location, race/ethnicity, and various social domains. The analysis investigated the role of both individual-level variables which include age, sex, race/ethnicity, age at diagnosis and stage at diagnosis and contextual-level variable including census demographics, socio-environmental, socio-cultural, education-level, spatial access to COGs hospitals and percentage of health insurance coverage in these disparities. The study also investigated the effect of race/ethnicity on overall survival of childhood cancer patients while mediated through socioeconomic status and spatial accessibility mediators. The study selected the state of Texas as the study area because of its diverse population group, especially third-largest Hispanic population (Hamilton et al. 2016) which provide a distinct opportunity to study childhood cancer disparities.

The study proposed a conceptual framework in order to address the childhood cancer disparities in Texas (Figure 1.1). This framework outlines a research trajectory in four major areas of interest: (a) selecting factors contributing to health disparities in cancer patients; (b) examining determinants of health disparities with respect to cancer continuum; (c) identifying vulnerable population group in a specified area; (d)

recommending intervention program in targeted areas for eliminating health disparities in cancer patients. Factors contributing to health disparities in cancer patients include individual, contextual and medical care factors. Disparities in health must be investigated by casting our spotlight on the determinants of different health outcomes in population level (Whitehead et al. 1992; Warnecke et al. 2008).

Population health and health disparities were discussed in terms of three primary level of determinants including distal, intermediate, and proximal (Gehlert and Colditz 2011). This study incorporated the childhood cancer stage at diagnosis (early-stage and late-stage) as distal determinants. Intermediate determinants are described as social interaction and the physical context of a neighborhood or community (Gehlert and Colditz 2011). In our conceptual model, standard statistical unit, census tracts are considered as intermediate determinants where distal effects are the experience in community level resulting from contextual variables. Finally, individual-level factors of the cancer patients accounted as proximal determinants.

Our future study will investigate maternal residential exposure to air toxicant and childhood cancer in offspring. Previous study suggests that environmental risk factor such as prior chemotherapy and high dose ionizing radiation is associated with childhood cancer incidences. Accurate measurement of such environmental exposure is still a major challenge that ultimately limits our understanding of how they impact on childhood cancer risk.

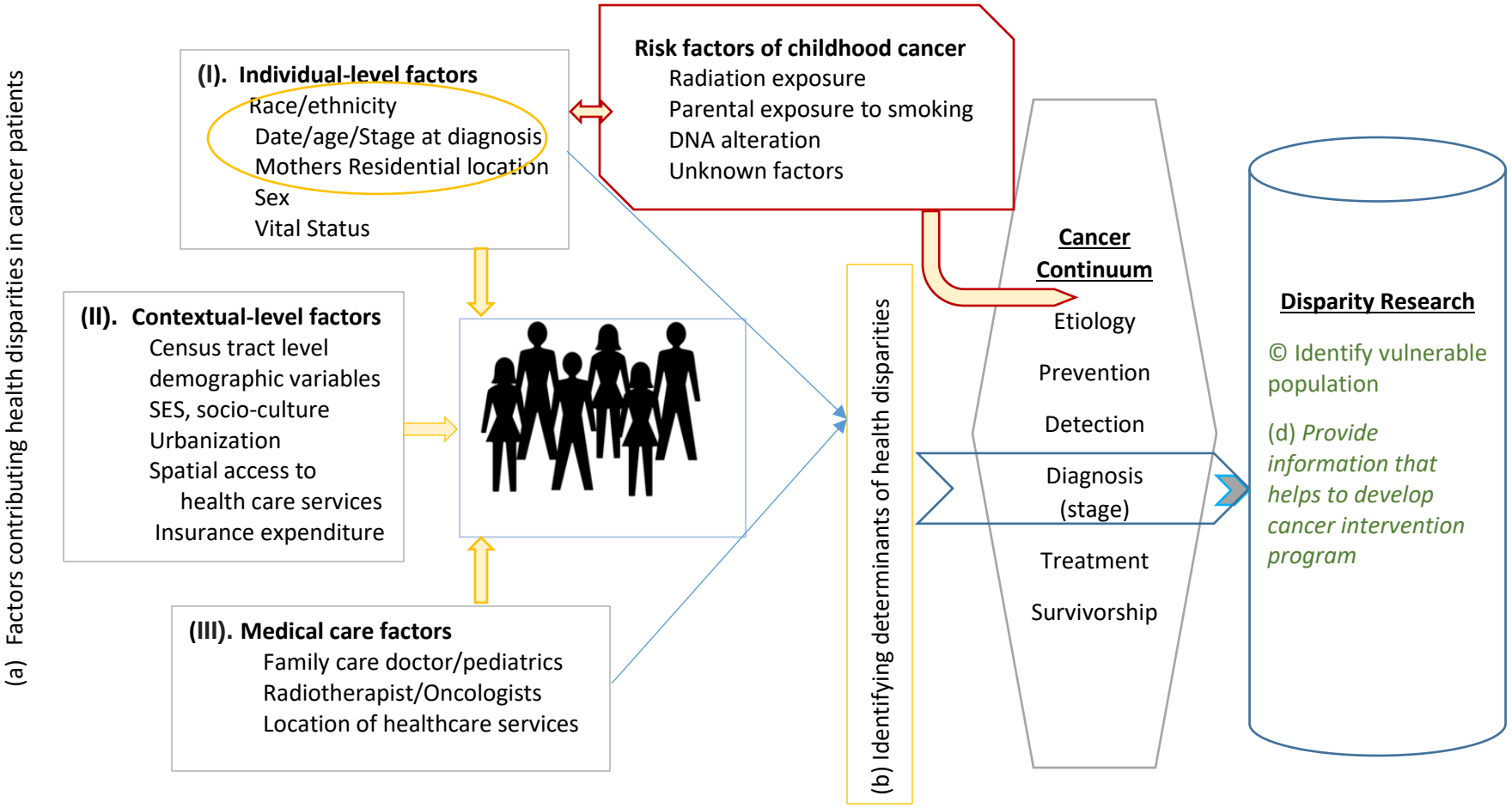

Figure 1.1 Conceptual framework of the childhood cancer disparities research

1.2 Problem Statement

The etiology of cancer has its spatial pattern (Thompson, Carozza, and Zhu 2007) but the geographical modeling of childhood cancer is challenging because of the dependency on their parents and other factors associated with it. The impact of geographic, racial/ethnic and social factors remains obscure for children with cancer. Despite the dedicated research on childhood cancer, the rigorous literature search comes up with some research gap on this rare disease in the United States, especially for Texas. First, few research has investigated the childhood cancer disparities from the perspective of geographic location and race/ethnicity. Second, no reported study has examined the spatial accessibility to specialized COGs hospitals from the perspective of the spatial distribution of demographic in census tracts. Third, no reported study in the United States has extensively investigated the impact of individual- and contextual- level factors associated with late stage diagnosis that hampers the cancer outcome significantly. Fourth, no reported study has investigated the underlying mechanistic pathways of race/ethnicity effect on overall survival for childhood cancer while mediated by socioeconomic status and spatial accessibility.

1.3 Objectives and Research questions

The following issues are addressed in this research:

I. Does the stage of childhood cancer at diagnosis vary by race/ethnicity, geographic locations and other social domains in Texas?
II. Is spatial access to COGs factor associated with the childhood cancer delay diagnosis?

III. How individual and contextual level factors impact the occurrence of the stage at diagnosis and its geographic pattern?

IV. Are there any geographic variations of racial/ethnic disparities in childhood cancer late-stage diagnosis in Texas?

V. Is there any effect of race/ethnicity on overall survival mediated by socioeconomic status and spatial accessibility?

According to the research objectives and the literature mentioned above, the following hypotheses were formulated:

Hypothesis 1: The stage of childhood cancer at diagnosis varies by race/ethnicity, geographic locations and other social domains in Texas.

Hypothesis 2: Spatial access to COGs factor is associated with childhood cancer delay diagnosis

Hypothesis 3: Individual level factors in conjunction with contextual level factors impact the occurrence of the stage at diagnosis and its geographic pattern

Hypothesis 4: There is a statistically significant geographic variation of racial/ethnic disparities in childhood cancer late-stage diagnosis in Texas.

Hypothesis 5: Race/ethnicity effect on overall survival while mediated through socioeconomic status and spatial accessibility mediators.

1.4 Childhood cancer disparity and Geography

In the simplest form of definition, Geography is the study of the Earth, humans' relationships with the earth, and peoples' relationships with one another-all of which vary across time and space (Clifford et al. 2009). It may come harder than one might expect when it comes to characterizing the core of geography. Geography has been shaped by

social science, physical science and humanities traditions. It has been shaped by the concepts which lie at the core of the discipline, and to how our changing world can make the best use of rich geographical knowledge. The key concepts that lie at the center of the discipline are space, place, time, scale, landscape, nature, systems, globalization, risk and development (Clifford et al. 2009). This unique characteristic of the discipline provides a handful opportunity to collaborate with other disciplines.

Four substantives research traditions make claims on where geography as a discipline based on place-space, physical environment, human environment, the mapping science (Turner 2002). These are the modified form of Pattison (1990) traditions of geography introduced in 1963. Traditionally, the researcher examines the occurrence and distribution of variability in various domain in order to understand the nature of physical and human existence. This examination involved exploring spatial distributions, pattern, and association, testing the effect of scale. The outcome of these exploration must be communicated by developing appropriate modes of representation (Cutter, Golledge, and Graf 2002). This study will use four traditions structure to demonstrate how childhood cancer disparity research fits in the broader geography literature.

Geographic thinking and reasoning have provided a basis for the understanding of where things are, what they are, and their spatial effect (Golledge 2002). The place-space tradition focused on discovering the pattern and distribution of spatial entities by analyzing their geometry and movement. Place-space tradition has improved significantly with the advent of Geographic Information Science (GIScience) associated with quantitative geography. Human environment tradition is also known as man-land tradition. This tradition concentrates on the mutual relationships between human and the

environment. Physical environment tradition always comes along with the human environment. Human geography can never be complete without its physical environment as it does with childhood cancer disparity research. This study includes individual and contextual level factors to examine disparity from the perspective of geographic location, race/ethnicity and socio-economic status (SES). Both human and its surrounding environment are at the center of the research design. Geographic distribution of an event or phenomenon falls under mapping science traditions. Diseases mapping summarizes the spatial variation of cancer outcomes in order to quantify the geographic disparities.

GIScience enabled us to create rich information databases, linked to spatial analysis methods, to determine relationships between disease distributions pattern and physical and social environmental conditions (Gerard Rushton, Elmes, and Mcmaster 1999). The ability of Geographic Information System (GIS) is improving because of the advancement in the quality of geospatial data, spatial analysis algorithms, and computer hardware. In the field of health geography or medical geography, GIS is used for diseases mapping, examining spatial pattern of diseases, identifying risk factor of spatial pattern, analyzing health care access, and locating health care services.

The impact of place on health is a key component of epidemiologic research. Generally, spatial health-related data are analyzed using spatial analysis method in case-control study design. The case-control study investigates the association between disease and potential risk factors. Samples are taken separately about diseased cases and of controls at risk of developing the disease (Ahrens and Pigeot 2014). The temporal aspect of GIS and health are also an important consideration for diseases like cancers to estimate the effect of a particular contributing factors that might increase the risk of disease. In

those circumstances, we need to predate by 10 to 20 years from the diagnosis of the diseases (Gerard Rushton, Elmes, and Mcmaster 1999). Geocomputation and spatial analysis with temporal effect are integrated into recent health geography and epidemiological studies.

2. LITERATURE REVIEW

2.1 Health disparity

The term health disparities originated from a complex interaction between patient, provider, and institutional factors (Murphy, Tseng, and Shah 2010). According to the Department of Health and Human Services (DHHS, 2000) health disparity as "population specific differences in the presence of diseases, health outcomes, or access to care." The National Institute of Health (NIH) plays a unique and vital role to eradicate health disparities in the United States. This institute recognizes health disparity as a concern for the whole nation rather than a "problem" for individual who is experiencing in practical (National Institutes of Health 2009). Several studies revealed that health disparities could be attributed to a large spectrum of contextual factors (i.e., demographic variables at census tracts level, access to health insurance, urbanization extent, and spatial access to Primary care physicians) operate beyond the individual factors (Lin, Schootman, and Zhan 2015; Holmes et al. 2008). It is not quite simple and straightforward to blame some counterpart responsible for this disparity. Rather we can discuss and talk about *who* and *what* factors drives social disparities in health and *how* we can address those societal, political and policy implications in general. In January 2000, the Department of Health and Human Services (DHHS) conferred a national goal, to "eradicate health disparities" with the banner of healthy people 2010 (Carter-Pokras and Baquet 2002).

2.2 Cancer disparity

Health disparity is evident from the literature about health and different disease which needs particular attention from a geographic perspective as well as the overall treatment process. For example, cancer disparities are well documented for racial/ethnic

minorities and low-income patients in detection, treatment, and outcomes (Smedley, Stith, and Nelson 2003). Cancer disparity research involves individual level cases which are subject to a breach of confidential information. The rules of human subject protection for institutional research was introduced in light of the misuse 'Tuskegee' study when the experiment was only conducted among blacks (Steinberg 2008). Once people get to know the fact, fear existed, and distrust arose in institutional medical research, the Belmont report (National Institutes of Health 1979) came to play an important role. Researchers understanding to epidemiologic study and the interpretation of medical outcomes based on race construct relationship has improved throughout the years (Steinberg 2008).

This research undertook a literature search in the database of Web of Science (WoS) of the Institute of Scientific Information (ISI). The keyword used for the search were 'childhood cancer,' or 'pediatric cancer,' and 'cancer disparity,' and 'cancer disparities.' A total of 28,402 publications were returned from this conditional search option. Figure 2.1 demonstrates the growing trend of childhood cancer or overall cancer disparity research.

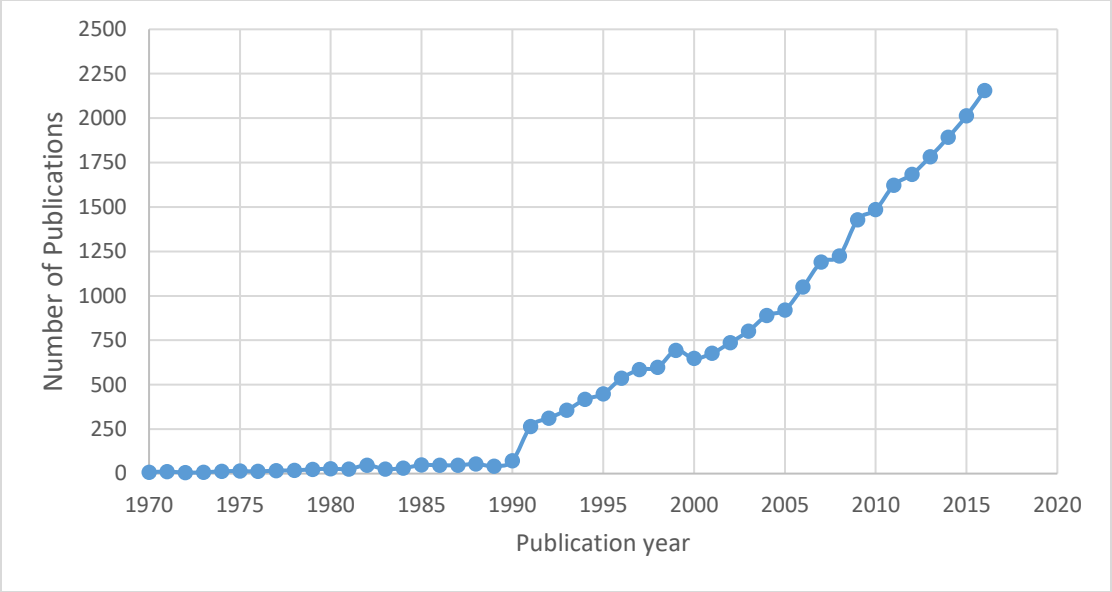

Figure 2.1 Number of publications on cancer disparities research each year based on data from WoS (as of September 26, 2017)

According to this thorough search, cancer disparity research goes back to 1940s'. There was a gradual increase in publications number each year till the 1990s'. However, there was a sharp increase in the number of publications since 1991, which ranges from 250 to more than 2000 per year. This sudden increase is attributed to the awareness of the scientific community about this popular topic. Individual researcher and relevant institutes from all over the globe are contributing to the domain of social inequality. In total, 136 countries/regions/former countries have published research on cancer disparity (Figure 2.2).

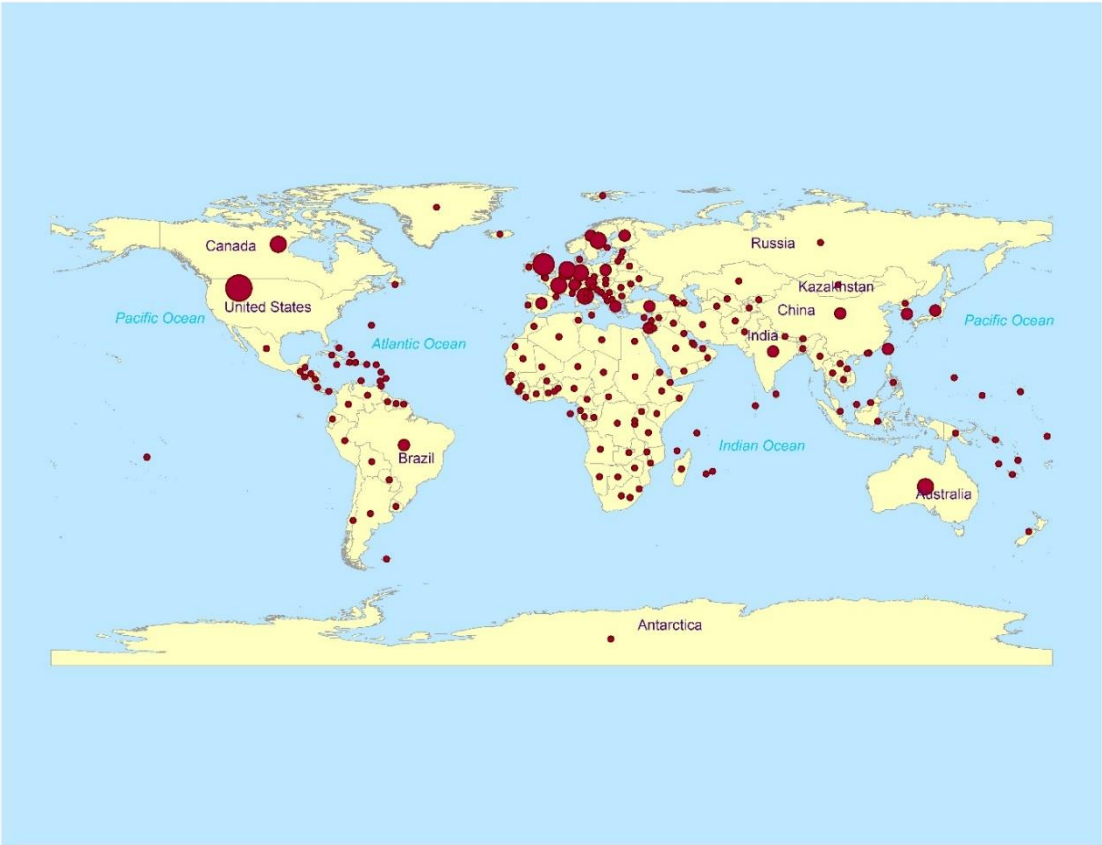

Figure 2.2 Geographic distribution of reported research about cancer disparities based on information retrieved from WoS databases as of September 25, 2017.

*The sizes of points are proportionate to the number of publications in the countries/regions/former countries.

The number of publications is not evenly distributed across the continents. Majority of the publication is from North America and Europe where the United States alone contributed 42.08 percent of the total publication. Table 2.1 shows the list of major countries with their percent contribution to cancer disparity research.

Table 2.1 Publication distribution of major countries of cancer disparity research

Countries/Regions	Records	Percentage	Countries/Regions	Records	Percentage
United States	11951	42.08%	China	764	2.69%
United Kingdom	3785	11.35%	Denmark	626	2.20%
Germany	2078	7.29%	Switzerland	570	2.01%
Canada	2001	7.05%	Spain	526	1.85%
France	1613	5.68%	Brazil	506	1.78%
Italy	1505	5.30%	Turkey	503	1.77%
Netherlands	1307	4.60%	India	439	1.55%
Sweden	1117	3.93%	Finland	426	1.50%
Australia	1076	3.79%	Israel	376	1.32%
Japan	951	3.35%	Austria	353	1.24%

There are a couple of possible reasons attributed to the clustered geographic distribution includes the data availability and completeness, People's awareness in different countries/regions/former countries, and available research facilities.

Significant research has already been done for race/ethnicity and socioeconomic status disparities (Krieger 2005; Read and Emerson 2005; Murphy, Tseng, and Shah 2010; Ward et al. 2010 and Borugian et al. 2011; Lin, Schootman, and Zhan 2015). Racial disparities for African-Americans and Hispanic woman were prominent in the case of breast cancer mortality compared to the non-Hispanics white in the case of rate difference measurement (Tian et al. 2010). Another study about cervical cancer revealed that African-American experienced higher mortality risk when the stage was unknown compared with non-Hispanic whites (Lin, Schootman, and Zhan 2015).

Selected publication on cancer disparities in the United States is described in table 2.2. The intersection of social inequality and cancer continuum were categorized into 'grid' format. This review found that most studies on cancer disparities focused on race/ethnicity and SES within the domain of social inequality, and incidence, screening, diagnosis, treatment, mortality, and survival within the cancer continuum. There is a

moderate number of research that focused on socio-cultural factors, insurance, and geography within the social inequality domain as well as screening and cancer treatment within the cancer continuum. There is little work on spatial access to health care, behavioral factor, socio-environmental factors, and healthcare provider.

Table 2.2 A review of selected publications on cancer disparities in the United States

Study	**Purpose**	**Cancer Site(s) continuum, and study period**	**Setting and scale**	**Domains of social inequality**	**Conclusion**
(Abraho et al. 2016)	To examine the trend in early death and survival	Survival and mortality of acute myeloid leukemia, 1988-2011	California individual level	Race, SES, and insurance	Mortality rate with AML is high in California and increases with age
(M. T. Austin et al. 2015)	To examine health disparities in cancer cases and their impact.	Non-CNS solid tumors malignancies, 1995-2009	Texas individual level	Race and SES	Hispanics and non-Hispanics black exhibited significant disparities compared to their counterpart.
(Bona et al. 2016)	To investigate the impact of SES on incidence and survival	ALL consortium protocols, 2000-2010	US children with ALL	Race and SES	Despite uniform treatment, SES is an important predictor of childhood cancer outcomes
(Fluchel et al. 2014)	To examine the impact of cancer treatment based on rural/urban residence and travel time on social domains	Pediatric cancers, 2010-2012	7 States, US Individual level	Geography, SES, insurance, spatial access to health care	The greater burden for the patients who lives far away from the treatment center.
(Grubb et al. 2016)	To examine the association between demographics, diseases, treatment characteristics with Overall survival	Hodgkin Lymphoma Survival 1981-2010	Florida Individual level	Race/ethnicity	Racial disparities existed in overall survival between blacks, whites, and Hispanics.
(Hamilton et al. 2016)	To examine health disparity in melanoma patients affecting disease presentation and outcomes	Children with melanoma, 1995-2009	Texas individual level	Race, SES, and access to health care	Disparities exist in disease presentation and overall outcome of pediatric patients with melanoma.

(Hord et al. 1996)	To compare treatment outcomes to different ethnicity.	ALL, 1974-1985	Texas, individual level	Race and SES	Cure rate and event-free survival of Mexican-American are less than European-American.
(Kadan-Lottick et al. 2003)	To examine disparities in survival by race and ethnicity	ALL, 1973-1999	9 SEER sites	Race	Improvement in treatment service on survival from ALL varies by racial and ethnic group.
(Kent et al. 2009)	To examine SES and survival relationships concerning race/ethnicity	Leukemia, 1996-2005	California, individual level	Race, SES, and insurance	AYA had lower survival and effect of lack of insurance and low SES varied across races
(Kirchhoff et al. 2014)	To investigate the racial disparity of AYA cancer survivors	Cancer survivors, 2009	US, Individual level	Race, SES, and insurance	Hispanics survivors had the poorest general health whereas other groups reported fair to poor health,
(Knoble, Alderfer, and Hossain 2016)	To examine the association between community-level SES indicators and mortality of AML patients	Survival and mortality of AML pediatric patients 1973-2012	US population-based SEER 17	Race, SES, and Immigration status	Survival advances in pediatric AML research are not benefiting equally to all children.
(Metzger et al. 2008)	To investigate the effect of race on clinical outcome	Hodgkin's Lymphoma 1990-2005	US, Individual level	Race and insurance	Though both groups had the same 5-years overall survival, blacks had lower event-free overall survival.
(Okcu et al. 2002)	To investigate the racial disparities in cancer incidence in relation to birth weight.	Childhood cancer, 1995	Texas Individual level	Race and behavioral factors	Increased ALL risk is found associated with birth weight in early childhood.
(Pagaoa et al. 2011)	To examine the association between vaccination and childhood cancers	Childhood cancers. 1995-2006	Texas Individual level	Race and SES	Hispanics had a higher risk of developing ALL compared to whites and blacks.

(Peckham et al. 2015)	To examine the association between indoor radon exposure and Cancer, and their disparity	Childhood lymphoma, 1995-2011	Texas Individual level	Race and geography	Not a significant association between residential radon exposure and Childhood lymphoma.
(Pui et al. 2012)	To determine the disparity in cancer outcomes in whites and blacks	Pediatric cancer, 1992-2007	SEER, individual level	Race	Cure rates can be improved for both cases by ensuring equal access to comprehensive treatment
(Thompson, Carozza, and Zhu 2008)	To identify geographic risk pattern of multiple cancer types	Multiple cancer types, 1990-2002	Texas County level	Geography and sociocultural factors	Geographic factors support further study of four cancer types in several counties.
(Thompson et al. 2010)	To identify specific watersheds of mother's living location and their association with cancer	Childhood cancer, 1990-2002	Texas watersheds boundary	Geography	Increased risk specific types of childhood cancer were found associated with nine watersheds in Texas
(Tian, Wilson, and Zhan 2011)	To investigate racial/ethnic and SES disparities in diagnosis and mortality	Breast cancer late-stage diagnosis and mortality, 1995-2005	Texas, individual level	Race and geography	Racial/ethnic disparities existed in late-stage diagnosis and mortality, also vary by region.
(Wan, Zhan, Zou, et al. 2012)	To examine variation in spatial access to race, SES groups, and geographic region	Colorectal cancer, 2000	Texas, Census tract level	Race, SES and spatial access to health care	Unequal spatial access was found in racially/ethnically diverse population living in rural-urban characteristics.
(Ward et al. 2010)	To investigate racial/ethnic disparities in cancer incidence, survival, and mortality	Cancer data for two racial groups: 1975-2000; 1992-2000	US-population based, SEER 11	Race, SES, and health insurance	The racial disparity exists in cancer survival, and poor neighborhood had a lower survival rate.
(Whitworth, Symanski, and Coker 2008)	To examine the disparity in cancer accounting for hazardous air pollutants.	Childhood cancer, 1995-2004	Texas Individual level	Race and SES	Hispanics had a higher incidence in ALL and AML whereas Hodgkin disease and NHL cases in whites.

2.3 Childhood cancer disparity

Cancer types are often different in children compared to the types that develop in adults. Cancer in children are the consequences of DNA changes in cells that take place very early stage of their life, sometimes even before birth. Cancer survivors have increased throughout the years because of improved diagnostic procedure, therapy and above all supportive care to the cancer community (Armenian et al. 2013). In the western world childhood cancer is the leading cause of death and more specifically in the United States, the childhood cancer is the second leading cause of mortality among children (Jemal et al. 2008). In the modern history of the risk-stratified era, the role of race/ethnicity in the survival of childhood cancer is vague. Some studies support poorer survival in minority group whereas others reported equivalent survival in racial groups. For example, Pollock et al. (2000) performed a retrospective analysis of the pediatric oncology group therapeutic trial of 5,086 children (4,061 white, 518 black, and 507 Hispanic) between 1981 and 1994. According to this study 5-year overall survival rates were 81.9% ± 0.6%, 68.6% ± 2.1%, and 74.9% ± 2.0% for whites, Hispanics, and blacks respectively. When age was adjusted black, and Hispanics children had an excess amount of mortality which is 42% and 33% compared to white. One of the overarching goals of the American Cancer Society in 2015 was to eliminate disparities in cancer burden (Byers 2010).

The review used Incidence, screening, diagnosis, treatment, survival, and mortality as the cancer continuums. Table 2.3 incorporated race/ethnicity, SES, socio-cultural factors (such as immigration status), spatial access to health care, insurance, socio-environmental factors (such as the percentage of Hispanics and African

Americans), behavioral factors, and health care provider within the social inequality domain. Most of the disparity research focus quantitative analysis of the incidence, diagnosis, and mortality of racial/ethnic minority group and other population.

Table 2.3 Childhood cancer disparities grid

Domain Social inequality	**Cancer continuum**				
	Incidence	**Diagnosis**	**Treatment**	**Survival**	**Mortality**
Race/ethnicity	(Chen et al. 2006) (Danysh et al. 2016)(Kent et al. 2009) (Okcu et al. 2002) (Piwkham et al. 2011)(Reynolds et al. 2005) (Senkayi et al. 2014) (Ward et al.2014)(Whitworth, Symanski, and Coker 2008)	(Haimi 2004) (Stefan and Siemonsma 2011) (Martin et al. 2007)(Brad H. Pollock, Krischer, and Vietti 1991)	(Fluchel et al. 2014; Metzger et al. 2008)	Abrahao et al. 2015 Armenian et al. 2013; Austin et al. 2015; Hord et al. 1996; Kadan-Lottick et al. 2003;(Kent et al. 2009) Park et al. 2005; Pui et al. 2012; (Ward et al. 2014)	(Abraho et al. 2016) Goovaerts, Meliker, and Jacquez 2007; Metzger et al. 2008; Ward et al. 2014)
Socioeconomic status	(H. D. Bailey et al. 2011) (Chen et al. 2006) (Cordier et al. 2001)(Dang-Tan et al. 2010)(Danysh et al. 2016) (Feller et al. 2010) (Howard et al. 2008)(Kent et al. 2009)	(Abdelkhalek et al. 2014)(Brad H. Pollock, Krischer, and Vietti 1991) (Dang-Tan et al. 2010) (Martin et al. 2007) (Patel et al. 2016) (Stefan and Siemonsma 2011)		Abrahao et al. 2015; Adam et al. 2016; Austin et al. 2015; Gupta et al. 2014; Gupta et al. 2014;(Kent et al. 2009) Park et al. 2005	(Abraho et al. 2016) (Howard et al. 2008)
Immigration status	(H. D. Bailey et al. 2011) (Greenop et al. 2015)			(Hord et al. 1996) (Knoble, Alderfer, and Hossain 2016)	(Knoble, Alderfer, and Hossain 2016)

Geography	(Cordier et al. 2001) (Danysh et al. 2016) (Howard et al. 2008) (Stiller 2004) (Thompson, Carozza, and Zhu 2008)	(Abdelkhalek et al. 2014) (Dang-Tan et al. 2008) (Dang-Tan et al. 2010)(Martin et al. 2007)	(Dang-Tan et al. 2008) (Fluchel et al. 2014)	(Gupta et al. 2014)(Warner et al. 2014)	Bosetti et al. 2010; Gupta et al. 2016; Howard et al. 2008)(Knoble, Alderfer, and Hossain 2016)
Spatial access to health care				(M. T. Austin et al. 2015)(Gupta et al. 2014)	
Insurance	(Kent et al. 2009)	(Martin et al. 2007; Metzger et al. 2008)	(Fluchel et al. 2014) (Keegan et al. 2014)	(Abraho et al. 2016) (Kent et al. 2009) (Park et al. 2005) (Warner et al. 2014)	(Abraho et al. 2016)
Socio-environmental factor	(Chen et al. 2006) (Danysh et al. 2015; Greenop et al. 2015; Peckham et al. 2015; Senkayi et al. 2014) (Stiller 2004)(Thompson et al. 2010)(Whitworth, Symanski, and Coker 2008)				
Behavioral factors	(Okcu et al. 2002)				
Healthcare provider			(Araz and Guler 2015)	(Van Ryn 2002)	(Kent et al. 2009)

2.4 Childhood cancer scenario in Texas

In the United States each year in every million younger than 20 years of age, around 150 children and adolescents are diagnosed with cancer (Okcu et al. 2002; Ries et al. 1999). Texas ranked second in both area and population as an individual state in the United States. Cancer incidence and mortality varies geographically; studying of these two can provide important clues pertinent to healthcare access and etiology of the disease itself (Hsieh et al. 2009). Hsieh et al. (2009) suggested that nonmetropolitan counties are more prone to neuroblastoma mortality compared with metropolitan counties. They also mentioned that the incidence is on the rise which may attribute to the improvement of environmental factors, reporting system to demographic or SEER. Several other studies reported survival variability by race and ethnicity for different childhood cancer in the United States (Kent et al. 2009; Metzger et al. 2008; Kadan-Lottick et al. 2003; Bhatia et al. 2002). Figure 2.3 shows the childhood cancer average annual by ICCC-3 Group for the total 10 years period (2003 – 2012), in Texas. Brain, neural (iii-iv) scored the highest number in prevalence followed by leukemias (i) and lymphomas cancers (ii)

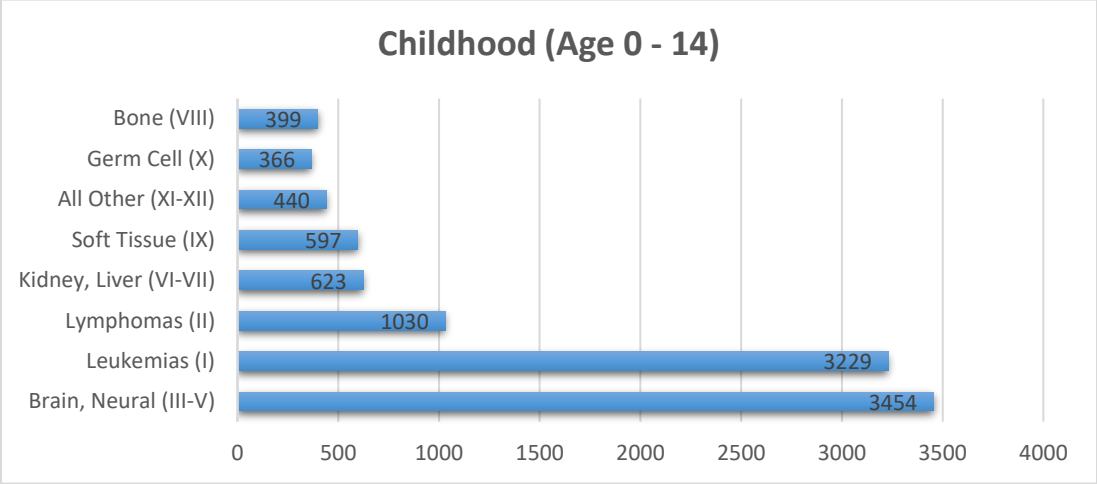

Figure 2.3 Childhood cancer average annual by ICCC-3 Group for the total 10 years period (2003 – 2012), in Texas.

* Rates are per 1,000,000 and age-adjusted to the 2000 US Standard Population
* Source: Texas Cancer Registry (www.dshs.state.tx.us/tcr) SEER*Stat Database, 1995-2012 Incidence, Texas statewide, Texas Department of State Health Services, created April 2015, based on NPCR-CSS Submission, cut-off 11/19/14.

Cancer prevention and treatment program requires resource allocation employing geographic modeling of cancer (Thompson, Carozza, and Zhu 2007; Short, Carlin, and Bushhouse 2016). Researcher from diverse background considered the state of Texas as their study location for childhood cancer research. For example, Studies considered Acute Lymphoblastic Leukemia in order to investigate the association of genetic variants (Piwkham et al. 2011); Ethnicity and cure rates (Hord et al. 1996); Socioeconomic status and event-free survival (Gupta, Sutradhar, et al. 2014). There are growing supportive evidence of a close association between childhood cancer and air pollution. Counties with rapidly growing population experienced high risk for Hodgkin lymphoma and malignant bone tumor whereas hepatic cancer near hazardous air pollutants, and germ cell tumors and “other” gliomas in places of high agricultural practice (Thompson, Carozza, and Zhu 2008).

Childhood cancer has been investigated for children living near airports (Senkayi et al. 2014); mothers' living location at the time of birth (Thompson et al. 2010); exposure to hazardous air pollutant (Whitworth, Symanski, and Coker 2008), Benzene (D'Andrea and Reddy 2014), residential radon (Peckham et al. 2015). A study by Okcu et al. (2002) reported an increased risk of developing childhood ALL during the first five years of life if the newborn weighed between 2500 and 4000 g at birth and children weighed > 4000 g. The childhood cancer incidence sequence by race/ethnicity was not explained by the difference in birth weight. Another study conducted by Pagaoa et al. (2011) suggested that black subjects had a lower risk of all cancer types combined whereas Hispanics showed a higher risk for development of ALL cancers compared with white subjects. Advance stage disease was predominant in Hispanics or non-Hispanics blacks, male, <10 years of old (M. T. Austin et al. 2015). Their study did not find a strong relationship on the stage of disease at presentation with socioeconomic status and distance to treatment facilities.

2.5 Late stage diagnosis factors

The principle goal in oncology is the early diagnosis of cancer since it permits an opportunity for timely treatment (Dang-Tan and Franco 2007). Childhood cancer diagnosis in its early stage can positively effect on prognosis (Abdelkhalek et al. 2014) and also impact on survival which certainly decreases the chance of morbidity (Araz and Guler 2015). There are main three factors that are attributed to delay in diagnosis for childhood cancer which includes patients and/or parent related factor, healthcare facilities and diseases itself (Dang-Tan and Franco 2007). This study used 'healthcare delay' as the physician delay or health system delay, more specifically the interval between the first

meeting with the primary doctor and diagnosis (Stefan and Siemonsma 2011). Delay in diagnosis also results from the rarity of the childhood cancer and non-specific exhibition of symptoms among the diagnostic group (Evans et al. 2014; Dang-Tan and Franco 2007). Also, patients and/or parents delay play a significant role in diagnosis delay.

The terms ‘patients delay’ and ‘parents delay’ are used interchangeably for delay diagnosis of childhood cancer as children are not able to make their decision for their well-being. In addition to children age and sex, parents’ age (Araz and Guler 2015; Haimi 2004), education level (Abdelkhalek et al. 2014; Ahrensberg et al. 2013; Stefan and Siemonsma 2011; Fajardo-Gutiérrez et al. 2002), socioeconomic status (Abdelkhalek et al. 2014; Araz and Guler 2015), race/ethnicity (Stefan and Siemonsma 2011; Haimi 2004)and family size (Araz and Guler 2015; Abdelkhalek et al. 2014) are considered as important factors for early stage diagnosis.

Table 2.4 demonstrates the patient-related or parent-related factors responsible for Diagnosis delay of childhood cancer. The patient's related factors which include age, sex, race/ethnicity, parental age, family size, socioeconomic status and parental level of education. Health care system related factors which include distance/community type, health professional visit that is responsible for delay diagnosis are described in table 2.5. Finally, table 2.6 describes the disease related factors that are responsible for delay diagnosis.

Table 2.4 patient-related or parent-related factors responsible for Diagnosis delay of childhood cancer

Variable	Authors	Study period	Analytical method	Summary P = .004	Concluding remarks
Age	(Abdel khalek et al. 2014)	2010 - 2012	ANOVA	P = 0.004	A significant correlation between age and total delay
	(Ahrensberg et al. 2013)	2007 - 2010	Logistic regression	p = 0.024	A significant association between age groups and diagnosis interval
	(Araz and Guler 2015)	2001 -2012	Chi-square test	P = 0.000	Significance with respect to middle versus the last child
	(Stefan and Siemonsma 2011)	2000 - 2009	spearman	r = 0.13, p = .08	Decrease total diagnosis delay with increase age of patients
	(Goyal et al. 2004)	1990 - 2002	Mann Whitney U	P = 0.05	Significant difference; older children face delay diagnosis. Significantly longer patient delay for Ewing's sarcoma
	(Rodrigues, Latorre, and de Camargo 2004)	1991 -2000	Mann–Whitney U	P = 0.001	Positive correlation; Diagnosis delay is shorter for children age < 24 mo compared to children > 24 mo.
	(Mehta et al. 2002)	1995 - 2000	Chi-square	P = 0.8	No significant difference
	(Dobrovoljac et al. 2002)	1980 - 1999	Pearson	r = 0.32; p < 0.0001	Positive correlation; older children at higher risk of diagnosis delay
	(Goddard, Kingston, and Hungerford 1999)	1993 - 1996	correlation Kruskal-Wallis	not mentioned	No significant difference in patients delay to age
	(Saha et al. 1993)	1982 - 1990	F test	P < 0.001	Significant difference; older children face longer diagnosis delay
	(Brad H. Pollock, Krischer, and Vietti 1991)	1982 - 1988	Pearson correlation	P < 0.001	Positive correlation; older children experienced longer diagnosis delay
Sex	(Abdel khalek et al. 2014)	2010 - 2012	*t* test	P = 0.901	No Significant association between sex and total delay
	(Araz and Guler 2015)	2001 -2012	Chi-square test	P > 0.05	No relationship between sex and total delay

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	(Ahrensberg et al. 2013)	2007 - 2010	Logistic regression	P = 0.755	Genders did not have a significant influence on diagnosis interval
	(Stefan and Siemonsma 2011)	2000 - 2009	Mann–Whitney U	P = 0.73	Sex does not show significant influence on total delay
	(Haimi 2004)	1993 - 2001	Student t	Not mentioned	No significance difference
	(Rodrigues, Latorre, and de Camargo 2004)	1991 - 2000	Mann–Whitney U	P = 0.949	No significant difference
	(Dobrovoljac et al. 2002)	1980 - 1999	Wilcoxon rank sum	Not mentioned	No significant difference
	(Mehta et al. 2002)	1995 - 2000	Chi-square test	P = 0.131	No significant difference
	(Saha et al. 1993)	1982 - 1990	ANOVA	1.2 (0.9-1.6)	No significant difference
	(Brad H. Pollock, Krischer, and Vietti 1991)	1982 - 1988	Student t	P = 0.18	No significant difference overall; longer delays for boys for Ewing sarcoma, and for girls for non-Hodgkin lymphoma only
Race/ethnicity	(Stefan and Siemonsma 2011)	2000 - 2009	Kruskal–Wallis	P = 0.90	The ethnicity of patients' didn't have a significant effect on total diagnosis delay
	(Haimi 2004)	1993 - 2001	Wilcoxon rank sum	$p < 0.05$	Shorter lag time for children of Arabic, Israel, Ashkenazi children than Sephardic fathers
	(Rodrigues, Latorre, and de Camargo 2004)	1991 -2000	Mann–Whitney U	P = 0.533	No significant association
	(Brad H. Pollock, Krischer, and Vietti 1991)	1982 - 1988	Student t	P = 0.23	No significance difference; While children experienced longer delay for osteosarcoma than nonwhite children.

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Family Size	(Abdel khalek et al. 2014)	2010 - 2012	ANOVA	P = 0.519	A significant association between family size and total delay
	(Araz and Guler 2015)	2001 -2012	Chi-square test	P > 0.05	No relationship between sibling number and total delay
Parents age	(Araz and Guler 2015)	2001 -2012	Chi-square test	P > 0.05	No Relationship between age of parent and parental delay
	(Haimi 2004)	1993 - 2001	F test	p < 0.01	Children of younger parents show shorter delays than children of older parents
Education level	(Adam et al. 2016)	1991-2006	Multivariate cox model	P < .05	Parents' education level was associated with survival from CNS tumors
	(Abdel khalek et al. 2014)	2010 - 2012	ANOVA	P < 0.001	A significant association between parent education and total delay
	(Ramírez-Ortiz et al. 2014)	2000-2010	Logistic regression	P < 0.05	Significant association with in predicting more advanced diseases
	(Ahrensberg et al. 2013)	2007 - 2010	Logistic regression	p = 0.656	No significant association between parental education and diagnostic interval
	(Stefan and Siemonsma 2011)	2000 - 2009	spearman	p = 0.92	Parents education did not have a significant influence on the total diagnosis delay
	(Brown et al. 2009)	2006 – 2008	Mann Whitney U	p = 0.496	No significant difference in lag time and parents with secondary education
	(Fajardo-Gutiérrez et al. 2002)	1981 - 1992	Logistic regression	OR (Father) 1.4; (Mother) 1.5	Long delays with low educated (0-5 years) parents compared to the parents with > 12 years education
Socioeconomic status	(Abdel khalek et al. 2014)	2010 - 2012	ANOVA	P < 0.001	A significant association between socioeconomic status and total delay
	(Araz and Guler 2015)	2001 -2012	ANOVA & t test	P = .022	A significant association between the socioeconomic status of family and total delay
	(Ramírez-Ortiz et al. 2014)	2000 - 2010	Logistic regression	P < 0.05	Significant association with in predicting more advanced diseases
	(Feller et al. 2010)	1991 - 2006	Logistic regression	0.773	

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	(Dang-Tan et al. 2010)	1995 - 2000	Logistic regression	Multiple results	No association between socioeconomic status and risk of all Family income significantly correlated with patients and HCS delays.

Table 2.5 Healthcare system related factors responsible for Diagnosis delay of childhood cancer

Healthcare factor	**Author**	**Statistical analysis**	**Results**	**Concluding remarks**
Distance/Community Type	(Araz and Guler 2015)	Chi-square test	P = 0.022	The long parental delay was more frequent patients living in rural areas than in urban
	(Abdel khalek et al. 2014)	ANOVA	P = 0.855	No significant association between residence and total delay
	(Dang-Tan et al. 2010)	Logistic regression	OR = 0.71 (95% CI)	Lower risk of health care service delay in leukemia patients living in urban areas
	(Klein-Geltink et al. 2005)	Logistic regression	Multiple results	No association for patients or physicians delay
	(Fajardo-Gutiérrez et al. 2002)	Logistic regression	OR = 1.5; 95% CI 1.4 – 1.8	Children who lived far away from Mexico City had a greater risk of time to diagnosis
Health professional visit	(Stefan and Siemonsma 2011)	Mann-Whitney U	P = 0.08	The positive relation between shorter physician delay and testing being done, not statistically significant
	(Cecen et al. 2011)	Univariate analysis	P = 0.001	Significant time to diagnosis was observed in patients who first contacted to specialist compared to other branches (except pediatrician)
	(Klein-Geltink et al. 2005)	Stratified analysis	P < 0.01	A significant difference in waiting time between oncologist to treated by initial health care

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	(Haimi 2004)	Kruskal-Wallis	Result not mentioned	Physician delay and diagnosis is shorter for children observed by pediatrician than a family physician or other specialist

Table 2.6 Diseases related factors that correlate with the diagnosis delay

Cancer factor	Authors	Study period	Statistical analysis	Results	Concluding remarks
Type of cancer	(Araz and Guler 2015)	2001 - 2012	Chi-square test	P < .05	Significant influence of the type of cancers to patient and physicians delay
	(Abdelkhalek et al. 2014)	2010 - 2012	ANOVA	P < 0.001	Significant difference in total delay for different cancer type
	(Stefan and Siemonsma 2011)	2000 - 2009	Kruskal-Wallis	P = 0.26	No significant association between type of tumor and total diagnosis delay
	(Cecen et al. 2011)	1999 - 2009	Univariate analysis	P = 0.023	Patients with a renal tumor, neuroblastoma, and STS had significantly shorter time TD than germ cell or retinoblastoma
	(Dang-Tan et al. 2010)	1995 - 2000	Logistic regression	OR, 0.67, 95% CI, 0.5-0.9	Decreased risk of patients delay was observed in patients without acute lymphoblastic compared with ALL patients
	(Dang-Tan et al. 2008)	1995 – 2000	Wilcoxon rank sum and Kruskal-Wallis	P = 0.0001	Significant variation in delay diagnosis across cancer types
	(Klein-Geltink et al. 2005)	1995 - 2000	Logistic regression	Multiple results	Type of cancer influenced the risk of patient and physicians delay in diagnosis
	(Haimi 2004)	1993 - 2001	F-test	Results not shown	Significant difference; longest delay for epithelial tumors (med. 13 wks.) and the shortest delay for Wilms tumors (median, 2.5 wks.)
	(Fajardo-Gutiérrez et al. 2002)	1981 - 1992	Logistic regression	Multiple results	Other types of cancer showed longer diagnosis in comparison to leukemia.

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Symptoms	(Abdel khalek et al. 2014)	2010 - 2012	ANOVA	$P < 0.05$	Patients with brain tumors experienced a greater delay in diagnosis compared with leukemia and GCTs (Germ cell tumors)
	(Stefan and Siemonsma 2011)	2000 - 2009	Not mentioned	Results not shown	Patients were not very sick, or symptoms did not seem very important
	(Reulecke et al. 2007)	1980 - 2004	X^2 test	$P < 0.05$	Tumors growth change are positively correlated with a shorter interval between diagnosis and symptom onset.
	(Klein-Geltink et al. 2005)	1995 - 2000	Univariate analysis	$P < 0.01$	Significant shorter interval for 10 -14 years children living further, and the onset of symptoms and the initial health care contact
	(Haimi 2004)	1993 - 2001	Kruskal-Wallis	Not shown	Significant shorter parents' delay when symptoms were rare compared with common presenting symptoms
	(Rodrigues, Latorre, and de Camargo 2004)	1991 -2000	Mann-Whitney test	$P = 0.014$	Significant diagnosis delay was observed in patients with strabismus in comparison to other symptoms (leukocoria or tumor)
Tumor location	(Araz and Guler 2015)	2001 - 2012	Chi - square test	$P = 0.089$	No significant difference in tumor location with respect to parental delay.
	(Cecen et al. 2011)	1999 - 2009	Univariate analysis	$P = 0.005$	Patients with abdominal tumor had significantly shorter time TD than other cancer type
	(Haimi 2004)	1993 - 2001	Kruskal-Wallis	$P < 0.01$	Abdomen (as low as 7 Wks.), skull, eye, and chest showed shortest lag time
	(Goyal et al. 2004)	1990 - 2002	Linear regression	$P = 0.002$	Patients with axile site tumors had longer physician delay than limb tumors patient
	(Mehta et al. 2002)	1995 - 2000	Chi-square	$P = 0.014$	A significant difference in diagnosis delay between tumor location in brainstem and non-brainstem

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	(Dobrovoljac et al. 2002)	1980 - 1999	Krsukal-wallis	Not shown	No significant difference
Cancer stage	(Araz and Guler 2015)	2001 - 2012	Chi-square test	P = 0.013	Patients with early-stage disease had a longer total delay than those in advance stage
	(Brown et al. 2009)	2006 - 2008	Mann-Whitney U	P = 0.296	No significant association between the presence of metastatic diseases and overall lag time
	(Wallach et al. 2006)	1963 - 2004	Logistic regression	Multiple results	No significant association; Diagnosis delay decreased over time in advanced group
	(Rodrigues, Latorre, and de Camargo 2004)	1991 - 2000	Mann-Whitney U	P < 0.001	Patients with localized diseases had a significantly shorter diagnosis delay compared with metastatic or advanced disease.
	(Saha et al. 1993)	1982 - 1990	F test	P = 0.23	No significant difference in mean lag time and stage of cancer
Tumor Histology	(Henderson et al. 2011)	2001 - 2009	X^2 test	P < 0.001	Unfavorable histology for black patients compared with white patents
	(Dobrovoljac et al. 2002)	1980 - 1999	Wilcox rank sum	Not shown	Negative correlation; Shorter delay in first growing tumors compared with slow growing tumors.
	(Mehta et al. 2002)	1995 - 2000	Chi-square	P = 0.006	Delay in diagnosis differ significantly between medulloblastoma and non-medulloblastoma
WBC count	(Saha et al. 1993)	1982 - 1990	2 * 2 table	P = 0.7	No significant association
Family history	(Araz and Guler 2015)	2001 - 2012	Chi-square test	P = 0.38	No significant association between parental delay and family history of cancer
	(Wallach et al. 2006)	1963 - 2004	Logistic regression	P < 0.001	A significant difference in DI between positive family history and negative family history.

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Proper cancer management depends on the early diagnosis because that leaves the opportunity of early stage treatment. On time treatment believed to have better prognoses which can ensure the quality of life. Reducing diagnosis delay is fundamental for cancer outcomes. Diagnosis delay seems to have confusing meaning. In order to have a better understanding of diagnosis, delay may be categorized into three broad areas: patients' delay, health care system related delay and diseases itself. Most of the studies in this review were retrospective cohort studies, and there were significant variations in the study design. Patients related delay is attributed to several factors including age, sex, race/ethnicity, family size, parents' age, parents' education level, and socioeconomic status.

Patient's age is an important factor for diagnosis delay. Studies from different parts of the world reported contradictory results for diagnosis delay subject to different age groups (Table 2.4). Diagnosis delay can be mediated quite significantly with the disease symptoms. For example, the diseases symptom may be more identifiable in younger children than older children with cancer. The study revealed a significant correlation between children age and diagnosis delay (Abdelkhalek et al. 2014; Ahrensberg et al. 2013). Several studies reported positive correlation which means diagnosis delay longer for older children comparted with younger children (Goyal et al. 2004; Rodrigues, Latorre, and de Camargo 2004; Dobrovoljac et al. 2002; Saha et al. 1993; Brad H. Pollock, Krischer, and Vietti 1991). This correlation may not entirely depend on the disease's symptom and characteristics. Younger children may be more affiliated with their parents which helps their parents to notice abnormality or early stage disease compared with older children who are a little bit reluctant to share their health

status immediately. Sometimes it also depends on the culture, level of education and socioeconomic status of the parents. However, two studies reported no significant difference in age and delayed diagnosis (Mehta et al. 2002; Goddard, Kingston, and Hungerford 1999). Gender didn't exhibit significant association with diagnosis delay (Araz and Guler 2015; Abdelkhalek et al. 2014; Ahrensberg et al. 2013; Stefan and Siemonsma 2011; Haimi 2004; Rodrigues, Latorre, and de Camargo 2004; Dobrovoljac et al. 2002; Mehta et al. 2002; Saha et al. 1993; Brad H. Pollock, Krischer, and Vietti 1991).

According to the review race/ethnicity did not have a significant effect on the delay diagnosis for childhood cancer (Stefan and Siemonsma 2011; Rodrigues, Latorre, and de Camargo 2004; Brad H. Pollock, Krischer, and Vietti 1991) except one study in northern Israel (Haimi 2004). This study revealed that children of the Sephardic father had a longer lag time in comparison with Israeli, Ashkenazi, or Arabic fathers. There are two contradictory results when it comes to the relation between family size and delay diagnosis. Araz and Guler (2015) suggested that a number of siblings do not have any association with delay diagnosis whereas another study in Egypt emphasized family size as an important factor (Abdelkhalek et al. 2014). Children of younger parents showed a shorter delay compared with older parents (Haimi 2004). However, another study suggested no significant association with the parent's age to delay diagnosis (Araz and Guler 2015).

Parent's level of education and socioeconomic status are closely related to each other and seem to have a significant association with delay diagnosis for children with cancer. Educated parents usually earn more money and hold good socioeconomic status.

It is expected to find parents who have a lower education level; their children may face delay diagnosis because of the lack of knowledge and awareness. A statistically significant correlation was observed between parental education and total delay (Abdelkhalek et al. 2014; Ramírez-Ortiz et al. 2014; Fajardo-Gutiérrez et al. 2002). However, another half of the studies suggested that parental education did not have a significant influence on the total diagnosis delay (Ahrensberg et al. 2013; Stefan and Siemonsma 2011; Brown et al. 2009).

Children had a greater risk of diagnosis delay living far away from Mexico city (Fajardo-Gutiérrez et al. 2002). Another study from Southeastern turkey suggested that parental delay was more frequent living in rural areas compared to urban area. In developing countries, health care facilities more advanced in the urban setting in comparison with rural areas. However, the study found no significant association between residence location and delay (Abdelkhalek et al. 2014; Klein-Geltink et al. 2005). Leukemia patients living in urban areas experienced a lower risk of health care service delay (Dang-Tan et al. 2010). Though it is not statistically significant, there is a positive relation between the testing being done and shorter physician delay (Stefan and Siemonsma 2011) in Africa. A significant difference in waiting times for children examined pediatrician than a family physician or other specialist (Cecen et al. 2011; Haimi 2004). Another study in Canada also supported that significant difference in waiting times between treated by an oncologist and initial care contact (Klein-Geltink et al. 2005).

The rarity of non-specific presentation of symptom made the childhood cancer diagnosis difficult. Cancer type effect substantially on delay even after considering the

effects of other covariates, for instance, age, gender and race/ethnicity (Dang-Tan and Franco 2007). Significant variation in delay diagnosis across cancer types (Araz and Guler 2015; Abdelkhalek et al. 2014; (Cecen et al. 2011; Dang-Tan and Franco 2007; Klein-Geltink et al. 2005). Patients without acute lymphoblastic observed a decreased risk of patients delay compared with ALL patients (Dang-Tan et al. 2010). Leukemia cancer showed a shorter delay diagnosis compared to other cancer types. Only one study did not find a significant association between type of tumors and total diagnosis delay (Stefan and Siemonsma 2011).

Cancer symptoms are very ambiguous, and misinterpretation by patients, parents, and physicians may cause to delay diagnosis. Patients with brain tumors and strabismus experienced a greater delay in diagnosis compared with leukocoria or tumor, and leukemia and GTC respectively (Abdelkhalek et al. 2014; Rodrigues, Latorre, and de Camargo 2004). Haimi (2004) reported that significant shorter delay when symptoms were rare in comparisons to common presenting symptoms. This suggests that rare symptoms easily get noticed by the patients and parents. Change of tumor growth was found positively correlated with a shorter interval between diagnosis and onset of symptom in a study from Germany (Reulecke et al. 2007). The most common symptom that shortened the interval between the symptoms onset and diagnosis was early morning vomiting. Stefan and Siemonsma (2011) suggested that when patients were very sick symptoms did not seem very important. According to Klein-Geltink et al. (2005), children aged 10-14 years of the age experienced a shorter interval on the onset of symptoms and health care contact.

The study found tumor location and stage had a significant association with the primary symptoms (Reulecke et al. 2007). Patients with an abdominal tumor had a significantly shorter delay in diagnosis compared with other cancer type (Cecen et al. 2011; Haimi 2004). Mehta et al. (2002) reported significant differences in diagnosis delay between tumor located in brainstem compred to non-brainstem. Another study conducted in the UK suggested that patients with axile site tumors had a longer pysician delay than patients with limb tumors (Goyal et al. 2004). Two out of five studies reported no significant assocaition between diagnosis dealy and tumor location (Araz and Guler 2015; Dobrovoljac et al. 2002). Patients with advance stage of cancer had significantly shorter diagnosis dealy compared with cancer in its earlier stage (Araz and Guler 2015; Halperin and Friedman 1996). Rodrigues, Latorre, and de Camargo (2004) suggested that localized diseases had a significantly shorter diagnosis delay compared with metastatic or advanced diseases. Presence of metastatic diseasaes and overall lag time did not show significant association with overall lag time. (Brown et al. 2009). Diagnosis delay decreasesed over time in the advance group (Wallach et al. 2006) where as Saha et al. (1993) had not found any association in mean lag time and stage of cancer.

There is growing evidence of significant asssocaiton in diagnosis delay and tumor histology. Mehta et al. (2002) reported that diagnosis delay differs signifiantly between medulloblastoma and nonmedulloblastoma. However, another study by Dobrovoljac et al. (2002) suggested a negative association between diagnosis delay and tumor histology; shoter delays in fast-growing tumors in comparison to slow growing tumors. Henderson et al. (2011) found unfavorable histology for black patients compared with white patients. Two studies found contradictory results in the case of family history to diagnosis delay.

Wallach et al. (2006) reported a significant difference in Diagnosis interval to the family history. On the other hand, Araz and Guler (2015) found no association between parental delay and family history of cancer. White blood cell (WBC) count did not show any association with delay diagnosis (Saha et al. 1993).

Awareness of cancer disparities has been increasing over the past decades. There are numerous research and surveillance activities from NCI (National Cancer Institute) which include the SEER program contributing to the knowledge of cancer disparities. Childhood cancer and associated diagnosis delay research are still in its rudimentary stage. In order to determine the diagnosis delay individual factor, epidemiological characteristics of the tumor, and biological profile of an individual are important. This research gap warrants for more studies to identify delay diagnosis factors and their potential impact on the prognosis outcomes of the patients. In order to eliminate disparities of cancer collaborative efforts are needed from the government, private and non-profit organization and the individual involved in cancer prevention initiatives. The intervention of early detection of childhood cancer can start from public awareness program which includes adults and children specially teenager, and physician.

2.6 Cancer disparities research method

Health disparity still a developing field of study because of its diverse nature of factors and variables, and their associated method of measurement. Selecting an appropriate method of health disparity may affect the direction and size of the disparities results. Keppel et al. (2005) outlined six significant issues that are closely related to health disparities measurement. Issues to be considered when measuring health disparities: (a) choosing a reference point from which to measure a disparity; (b) whether

selecting disparity measurement in relative or absolute terms; (c) disparity measurement in pairwise fashion or summary measure; (d) disparity measurement in terms of favorable or adverse event; (e) Choosing to weigh group; (f) considering inherent ordering in groups.

2.6.1 Measurement of geographic disparities

Statistical methods that use space and spatial relationships (i.e., distance, length, height, area, volume, centrality, orientation and other spatial characteristics of data) directly in their mathematical computations is called spatial statistics. Spatial statistics can assist not only in the search for a spatial pattern in geographic data but also for shape analysis, surface modeling and surface prediction, spatial regression, statistical comparisons of spatial datasets, statistical modeling and prediction of spatial interaction. Spatial epidemiology has three traditions which include disease mapping, diseases clustering, and geographical analysis of the correlations between diseases and risk factors.

There are several methods for the detection of spatial clustering. Kernel smoothing is one them which is used to represent spatial variability in the mean of a variable (T. Bailey and Gatrell 1995). The value at one particular location is the result of a weighted function, applies to the values in the neighborhood location, where higher weights implied to closer locations. This approach creates a smooth surface that portrays a regional variation in the underlying values. Though the surface facilitates a visual way to explore data, the assessment of the significance of peaks is limited to Monte Carlo simulation or other statistical methods that do not have much control for the likelihood of a Type 1 error (Rogerson 2001).

Besag and Newell (1991) proposed a three-way classification of methods to detect the presence of spatial clustering: global, focal and test for the detection of clustering.

Global tests are designed to provide a single statistic, which in turn measure deviation from a random pattern. These tests provide information about whether an observed clustering is significant. Additional information about the location and size of the cluster are not provided in this test. Quadrat and nearest neighbor statistics are the two earliest global methods, developed in the field of ecology where species are considered to be spatially random. The population is not spatially random, and this is why these tests are limited to disease mapping. More importantly, we cannot speculate that the distribution of diseases should be spatially random. Diseases incidence may depend on several confounding variables such as sex, age, occupation, income, and a host of other factors. The selected literature discussed the idea of global clustering in Diggle and Chetwynd's bivariate K-function (S. B. Austin et al. 2005; Bernstein et al. 2004; Diggle and Chetwynd 1991) and the Potthoff-Whittinghill method (Kleinschmidt et al. 2001; Potthoff and Whittinghill 1966).

Global statistics find a clustering that is significant; then interest lies to the regions responsible for the significance. Focused or local statistics are used to find crime around a liquor establishment and diseases cluster around an indicator. Hence, local tests are employed to evaluate whether cluster occurs around particular foci. There are several local statistics such as Getis-Ord Gi Statistic (Ord and Getis 1995), Local Moran Statistic (Moran 1950), Score statistic, Stone's test, and Tango's C_F Statistics. The Getis' Gi Statistic identifies those clusters of points with values higher in magnitude than one might expect to find by random chance. The output of the Gi function is a z score for

each feature. A high z score for a feature indicates its neighbors have high attribute values and vice versa. The higher (or lower) the z score, the stronger the association. Local spatial autocorrelation around a specified subregion is determined using Local Moran statistics (Moran 1950). Tango's C_F Statistics identifies clusters around pre-specified foci employing modified and generalized score statistics (Tango 1995). It is preferred to use area method when data are aggregated to an aerial unit for instance census tracts. Geographic analysis of the association between clusters and related factors are performed employing socio-cultural information from the area units. The major drawback of using area method is Modifiable Area Unit Problem (MAUP).

Test for the detection of clustering facilitates searching for significant spatial association with no prior idea of where and how large the clusters would be. This method is especially useful for detecting cluster of rare diseases when the distribution of cases throughout the population is homogeneous. The likelihood of finding cluster even in the smaller number of zones could contain a certain number of cases (k). Though the results strongly depend on the arbitrary choice of K, the method is computationally less intensive than the Geographical Analytical machine (GAM). GAM is also designed for point pattern analysis in epidemiological research that combines computational philosophy and geostatistical thinking with GIS. This technique search for a pattern in a point dataset without being unduly affected by predefined areal units or data error (Openshaw et al. 1987).

Fotheringham and Zhan's method (Fotheringham and Zhan 1996) differs from Openshaw's GAM method in two ways. In Fotheringham and Zhan's method, location and size of a circle are randomly selected within specified ranges, and the significance

test is employed using poison probability distribution. This method is considerably less computation intensive and independent on minimum cluster size. Spatial scan statistics (Kulldorff 1998) is the most common method for local cluster detection. This method scans the entire map for areas with high or low rates using a circle of different size and location. Spatial scan statistics identify most likely cluster and secondary cluster using maximum likelihood estimation and also evaluate their significance (Kulldorff 1998). This particular method avoids multiple testing that is common in some exploration analysis (Fotheringham and Zhan 1996; G Rushton and Lolonis 1996; Openshaw et al. 1987). In addition, this method does not require a user specified size of a cluster for the clustering process (Kulldorff 1998)

The clustering method is mostly spatial in nature. There are several other studies those employed space-time clustering of infectious diseases and cancers: Daggle's global space time K-function (McNally et al. 2008; Houben et al. 2006), and global space-time Knox technique (McNally et al. 2008; Houben et al. 2006; Theophilides et al. 2003). The updated scan statistics software is also compatible with temporal, spatial and space-time clustering (Lin, Schootman, and Zhan 2015; Wan, Zhan, Lu, et al. 2012a; Kulldorff, Huang, and Konty 2009; Kulldorff et al. 2005). The details of this method are found in chapter five.

2.6.2 Measurement of disparity by multiple factors

Health care analysis involves hierarchical data at different levels (i.e., hospital level, the physician level, and of course the patent-level). Regression analysis is a statistical tool for describing the relationship between a response variable and one or more explanatory variables. Like simple correlation analysis, simple regression predicts

about dependent variable, more specifically conceptualize the relation between two variables. Whereas, multiple regression involves models that have a single dependent variable and two or more predictor variables. It provides information on the relationship, the relative strength of each variable, strength as a group of the variable, the interaction effects between the predictor variables (Urdan 2017). Traditional health disparity measures fail to provide statistical significance of the results, whereas regression analysis identifies statistically significant disparity that does not occur by chance. Let, x denote a value of independent variables, γ denote the outcome variable. The expected value of Y, given the value of x, can be expressed as follows:

$$\mathrm{E}(Y|x) = \beta_0 + \beta_1 x \qquad 2.1$$

Where β_0 is the linear intercept in the linear regression, β_1 is the coefficient of the variable x. In order to represent the conditional mean of Y given x, let's use the quantity $\pi(x) = \mathrm{E}(Y|x)$. The univariate logistic regression model is as follow:

$$\pi(x) = \frac{e^{\beta_0 + \beta_1 x}}{1 + e^{\beta_0 + \beta_1 x}} \qquad 2.2$$

Where $\pi(x)$ is the probality of being a case ('1'). Now, the multivariate logistic regression (Hosmer and Lemeshaw 2000) can be formualted using logit function as follows:

$$\text{logit } [\pi(x)] = \beta_0 + \beta_1 x_2 + \beta_2 x_2 + \ldots . \beta_N x_N = \beta_0 + \sum_{i=1}^{N} \beta_i x_i, \qquad 2.3$$

Here β_i is the coefficient of ith independent variables. It is apparent from the equation (2.7.3) that the logit of the probability of an event given x is a simple linear function. Maximum likelihood procedure used to estimate the coefficient of the variable.

Logistic distribution has two essential benefits: first, this function is easy to use and extremely flexible; second, it provides meaningful interpretation for health research

especially clinical research. This method has been used to analyze multiple factors in childhood cancer outcomes that are categorical (i.e., stage at diagnosis, death, survival, etc.) (Dang-Tan et al. 2010; Keegan et al. 2014; Abraho et al. 2016; M. T. Austin et al. 2015). Nevertheless, the traditional multivariate logistic regression fails to account for correlation among individuals within the same neighborhood, and the geographic variation because of random effect. This is because it is a single level model. Multilevel logistic regression addressed these issues which are discussed in chapter five.

2.6.3 Measurement of spatial access to health care

From the perspective of city planner, accessibility has extensive effects on the development of land. The concept of land development and accessibility (Hansen 1959) can be related to the spatial accessibility of healthcare service for a community. Access to medical care can be defined as a person's ease of accessing these services that can bring the best possible outcome (Wan, Zhan, Zou, et al. 2012; US Department of Health and Human Services 2000). There are three main factors that influence the potential spatial access to health access to medical services. These factors are the location of the healthcare professional (supply), the residential location of the people (demand) (Rosenblatt and Lishner 1991) and travel cost between the population and location of the health professionals (Wan, Zhan, Zou, et al. 2012; Luo and Wang 2003).

There are several other factors which can influence the access to health care services which includes people's health condition, overall financial and socio-economic status, perception about health and health care services, and geographical accessibility (Aday and Andersen 1974). The term geographical accessibility refers to the function of the physical distance and time that must be traversed to receive health care (Aday and

Andersen 1974). Potential accessibility and revealed accessibility are the two major categories of health care accessibility. Potential accessibility means the actual use of health care services and revealed accessibility refers to the available medical service in an area (Joseph and Phillips 1984). These two broad categories are further divided into 2 * 2 matrix: spatial accessibility and non-spatial accessibility based on the spatial factors (i.e., geographic location, distances), non-spatial factors (i.e., age, sex, social class, income and so on) (Luo and Qi 2009; Joseph and Phillips 1984).

There are two components of spatial accessibility, namely availability and proximity (Luo and Wang 2003; Joseph and Phillips 1984). It is worth noting that, "high availability of services does not guarantee high accessibility because it depends on the proximity of the population to those services. Also, close proximity does not guarantee high accessibility because it depends on the proximity of the population competing for available services" (McGrail and Humphreys 2009). There are several methods to measure potential spatial access to medical services which includes regional availability model, Kernel density model and gravity based model before the evolvement of floating catchment area (FCA) model.

The regional availability approach is often expressed as population-to-practitioner ratio within a region. This method is simple and measures the distribution of supply versus demand of that region (Luo and Wang 2003; Joseph and Phillips 1984). There are some problems associated with the regional availability approach because of the spatial distribution of supply and demand, competition between consumer and supplier, and their likely overlapping issue. Kernel density models estimate supply and demand surface by employing a kernel function. Potential spatial access is then calculated by dividing the

supply surface by the demanding surface. Distance decoy function in kernel density model could address the issue in regional availability method. Kernel density model itself suffers limitations of considering the influencing area of medical sites and the distribution of the population.

The gravity-based model was proposed by Hansen (1959), widely used to measure the spatial accessibility to medical services. This model considers nearby physician is more accessible than the distant one, thus weighted higher. According to this model accessibility (A_i^H) at location i:

$$A_i^H = \sum_{j=1}^{n} S_j \, d_{ij}^{-\beta} \qquad 2.4$$

Where n is the total number of physician locations, S_j is the number of physicians at location j, the travel time between population location i and physician location j is defined by d_{ij}. β is the travel friction coefficient.

There is a limitation in equation 2.4 because it only considers the physician location (supply). It does not consider the resident location (demand) which is the population competition to get the service. This method was further developed by Weibull (1976) taking into account the demand side of the model too. Here is the updated gravity-based accessibility measure (Luo and Wang 2003) at location i:

$$A_i^G = \sum_{j=1}^{n} \frac{S_j \, d_{ij}^{-\beta}}{V_j}, \qquad 2.5$$

Here, $V_j = \sum_{k=1}^{m} P_k d_{kj}^{-\beta}$,

Here, m is the total number of population locations, and gravity based index of accessibility is denoted by A_i^G. d_{ij} and d_{kj} are the distance or travel cost. The definition of n, S_j, β, i, j are mentioned in equation 2.1. The population size at location k is defined

by P_k. It is worth noting in relation to previous accessibility measure, A_i^H, the service competition intensity based on the availability of a physician is discounted A_i^G at location, V_j , measured by its population potential. The larger the A_i^G, the better the accessibility. Though this method seems conceptually complete, it suffers limitations to interpret intuitively and include more data into consideration (Luo and Qi 2009). Additionally, Huff (2000) suggested that friction coefficient (β) has to be evaluated by physician-patient interaction.

The two step floating catchment area (2SFCA) method is a special case gravity model which was proposed, which was first proposed by Radke and Mu (2000). This method uses the full advantage of the gravity-based model and easy to interpret. It accounts for a special form of physician to population ratio. There are two steps to follow to implement this method (Luo and Wang 2003). First, for each medical service location j, search all population locations (k) within a threshold travel time (d_o) from j, and compute the supply to demand ratio, R_j, within the catchment area:

$$R_j = \frac{S_j}{\sum_{k\in\{d_{kj}\le d_o\}} P_k} \qquad 2.6$$

Here, S_j refers to the health care capacity at locations j, and the travel time between $i\ and\ j$ refers to as d_{kj}. In the second step, search all physician location (j) for each population location i, within the threshold travel time (d_o) and catchment area i. The following expression defines the second step:

$$A_i^F = \sum_{j\in\{d_{ij}\le d_o\}} R_j = \sum_{j\in\{d_{ij}\le d_o\}} \frac{S_j}{\sum_{k\in\{d_{kj}\le d_o\}} P_k} \qquad 2.7$$

Where A_i^F is the spatial accessibility of population at location i, to the physician based on the 2SFCA method. The larger the A_i^F, the higher the accessibility for the population to

physician. Although number a of recent studies already employed 2SFCA method to measure health care accessibility (Wang and Roisman 2011; McGrail and Humphreys 2009; Yang, Goerge, and Mullner 2006), it suffers from two limitations (Luo and Qi 2009; McGrail and Humphreys 2009). First, all population within the catchment assume to have equal access, meaning distance decay within the catchment are not considered. Second, the dichotomous measure of the method which means all locations outside of the catchment have no access at all. The reality is people living in rural areas tend to travel longer distance and time to get health care compared to those living urban area, thus catchment also differs in those neighborhoods (McGrail and Humphreys 2009).

Enhanced 2-step floating catchment area (E2SFCA) method (Luo and Qi 2009) which apply weights to differentiate travel time zone in both steps, thus accounting for distance decay. The details of this method are found in chapter five.

2.6.4 Evolvement of Survival analysis

The average prognosis of cancer patients at the population level are measured using relative and cause-specific survival (Skyrud, Bray, and Møller 2014). The ratio between the observed and expected rates is termed as relative survival (RS) estimates, and it accounts for the death of all causes. On the other hand, cause-specific survival estimates are computed directly from information provided in death certification specifying the underlying cause of death, caused by the cancer of interest. This measure use follow-up information collected from the date of cancer diagnosis to the date of death, loss-to-follow-up or the end of the study period.

Kaplan and Meier (1958) estimator or the Cox (1972) proportional hazard regression were a commonly used method for measuring cause-specific survival. There

are some basic parameters in use when modeling survival data. Let's consider X (variable from a homogeneous population) is the time until some specified event (i.e., death, the development of some diseases, the appearance of a tumor, cessation of smoking, remission after some treatment, conception and so on). The distribution of X can be characterized in four functions : (a) survival function refers to the probability of an individual surviving to time *x*; (b) the hazard rate or risk function is the chance an individual of age x experience the event in the next in time; (c) the mean time to the event of interest, given the event has not occurred at x, is termed as mean residual life at time x; and (d) the probability density or probability mass function refers to the unconditional probability of the event's occurring at time x (Klein and Moeschberger 2003). Once we can evaluate one of these functions, then the rests can be uniquely determined.

Survival function is used to describe time-to event phenomenon employing basic quantity measure. The probability of an individual surviving beyond time x can be defined by the following expression:

$$S(x) = \Pr(X > x), \qquad 2.8$$

The observed time of a sample with size X sample is defined as: $0 \leq x_1 \leq x_2 \leq x_3 \leq \cdots x_N$, and $S(x)$ can be estimated by the following Kaplan and Meier (1958) estimator:

$$\hat{S}(x) = \prod_{X_J<X} \frac{n_j - m_j}{n_j} \qquad 2.9$$

Where, n_j and m_j represent the total number alive prior to time X_J, the total number of deaths at time X_J. It is worth noting that, if there is censoring n_j denotes the difference between the total number of alive cases and censored cases. However, if there is no censoring n_j represents the total number of alive cases prior to time X_J. The Kaplan-

Meier method suffer from one limitation because it estimates survival based on single factor.

In another way, the survival function acts as the complement of the cumulative distribution function when X is a continuous random variable, meaning that:

$$S(x) = 1 - F(x)$$

Where, $F(x) = Pr(X \leq x)$, $F(x)$ is a non-negative function with the area under $F(x)$ being equal to one. In the United States, the Department of Health and Human Services publishes state based yearly survival curves for all causes of mortality by race and sex in their vital statistics.

Cox proportional hazard model also estimates the survival. It is also called multiplicative hazard model. The basic model is as follows:

$$h(t|\boldsymbol{Z}) = h_0(t)c(\beta^t \boldsymbol{Z}) \quad 2.10$$

Where $h(t|\boldsymbol{Z})$ is the hazard rate at time t for an individual with risk vector $\boldsymbol{Z}$. $h_0(t)$ refers to arbitrary baseline hazard rate, $\beta = (\beta_1, \beta_2 \ldots\ldots\ldots \beta_p)^t$ is a parametric vector, and $c(\beta^t \boldsymbol{Z})$ is a known function. The model is semiparametric because the covariate effect only accounts in parametric form (Klein and Moeschberger 2003). In this model $h(t|\boldsymbol{Z})$ must be positive, so the baseline hazard rate is treated nonparametrically. The expression for $c(\beta^t \boldsymbol{Z})$ is as follows:

$$c(\beta^t \boldsymbol{Z}) = \exp(\beta^t \boldsymbol{Z}) = \exp\left(\sum_{k=1}^{p} \beta_k Z_k\right) \quad 2.11$$

Which yields, $h(t|\boldsymbol{Z}) = h_0(t) \exp\left(\sum_{k=1}^{p} \beta_k Z_k\right)$ 2.12

Cox proportional hazard model has both merits and demerits. The merit is no assumption on the shape of the underlying hazard, and the demerit is model assumes the impacts of covariates on hazard remain constant during the study period. Traditional cox

proportional hazard model also lacks to account for the random effect caused by geographic variation and correlations among individuals within the same neighborhood. Multilevel survival model takes into accounts those problems discussed above, and several studies (Lin, Schootman, and Zhan 2015; Schootman et al. 2009; Chaix, Rosvall, and Merlo 2007) have used this method. The details of this method are found in chapter six.

2.7 Limitations in childhood cancer disparity research

In the last several decades, a growing body of literature has adopted cancer disparity as a research topic. This topic has gained significant attention to scientists from all over the world (Figure 2.2). Childhood cancer disparity research uses individual level confidential information that includes the maternal residential address of each case and control. The major risk would involve a breach of confidentiality, allowing for identification of the patient. The researcher has to be extra cautious in handling dataset and publishing results. Cancer in children is rare, and its literature also lacks resources from different perspectives. This literature review has found the following limitations in childhood cancer disparity research:

First, because of the diverse population group and large geographic area, Texas is ideally suitable for cancer disparity research. Although there is cancer disparity research (Lin, Schootman, and Zhan 2015; Wan, Zhan, Lu, et al. 2012b; Tian, Wilson, and Zhan 2011), no study has examined childhood cancer disparities from the perspective of geographic location, race/ethnicity, and SES.

Second, cancer disparity research using a small sample size dispersedly located in a limited geographic area such as census tracts is a major challenge. Additionally,

childhood cancer is a rare disease, and there are usually a few cases in a small area unit. Problems arise during the analysis due to the lack of statistical power. There is a research gap to measure spatial variation of childhood cancer disparities in Texas based on census tracts.

Third, disparity analysis by making the appropriate method of measurement choice is a challenging task. Keppel et al. (2005) discussed six significant issues to be considered in disparity research. They also provided 11 (eleven) specific guideline to justify each method of interest. This study will use two test statistics such as relative (Risk Ratio, RR) and absolute (Risk difference, RD) measures (Goovaerts, Meliker, and Jacquez 2007).

Fourth, justifying the selected factors (i.e., race/ethnicity, SES) are also crucial for health disparity research (Polite et al. 2017). For example, cancer data lacks individual level SES data. Most of the study use area-level SES indicators are often aggregated at various geographic units (i.e., census tract or census block). In reality, SES is measured based on income level, poverty, education status, and housing condition. This is why ecological fallacy is obvious when inferring about an individual based on cancer disparity results at the population level. In those circumstances, it is recommended to use a small area unit such as census tract where population characteristics mostly homogeneous.

3. DATA AND METHODOLOGY

3.1 Data source:

This dissertation research included several data sources to collect individual-level childhood cancer incidence data, vital data, healthcare data, treatment data, and census data.

3.1.1 Childhood cancer incidence data

Childhood cancer incidence data of Texas from 1995 to 2014 was collected from the Texas Cancer Registry (TCR). This dataset is only limited to cases of individuals age between 0 to 19 years. TCR dataset includes sex, race/ethnicity, date of birth, mother's residential address, date of diagnosis, year of diagnosis, age at diagnosis, stage at diagnosis, primary site, tumor grade, vital status, follow-up source, date of the last contact, and cause of death. The stage at diagnosis is categorized into localized, regional, and distant stages based on the classification method from the Surveillance Epidemiology and End Result (SEER) program from the National Cancer Institute.

3.1.2 Childhood cancer medical service data

Childhood cancer medical service data was collected from the Children's Oncology Group database supported by National Cancer Institute (NCI). Major childhood cancer treatment centers are members of the Children's Oncology Group (COG) in North America, Australia, New Zealand, and Europe. There are 15 specialized childhood cancer service centers in Texas. Pediatrician and family doctors are often the first to suspect cancer based on the child's symptoms. Then they recommend them to the major childhood cancer treatment facilities where they receive service from staff with

special training to diagnose and treat children with cancer. There are around 9,390 family doctors and 6,463 pediatricians in Texas.

3.1.3 Census demographic data

Demographic data based on census tracts were collected from census 2010 datasets. This study used several variables to represent three major social domains: socio-economic, socio-cultural and socio-environment. The rate of employment, poverty rate, income, parent's education levels are considered as the SES indicators in some literature (Park et al. 2005; Bona et al. 2016; Hamilton et al. 2016; Knoble, Alderfer, and Hossain 2016). Socio-cultural data is represented by the percentage of linguistically isolated households from Summary File 3 (SF3) and percentage of foreign-born female form SF4. Socio-environment represented by population by age and race/ethnicity, the percentage of African American, the percentage of Hispanics will be extracted from census 2010 SF1.

3.1.4 Health insurance expenditure data

Health insurance expenditure data were collected from the American Community Survey (2006-2010). Health insurance expenditure variables include average household health insurance expenditure and average household commercial health insurance expenditure.

3.1.5 Treatment data

TCR provided childhood cancer incidence data enlisted individual-level treatment data which includes: treatment initiation date, surgery type, reason for no surgery, types of radiation treatment, reason for no radiation, sequence of radiation and surgery, chemotherapy at first course of treatment, hormone at first course of treatment, immunotherapy at first course of treatment, other treatment (not surgery, radiation, or

systematic therapy), and hematologic, transplant, and endocrine procedure at first course of treatment.

3.2 Protection of Human Subjects

The application for Childhood cancer incidence data and vital data was approved by the Texas Department of State Health Service (TDSHS) Institutional Review Board (IRB). The IRB review involved an agreement between TCR, CHS, and data user to ensure the confidentiality of the human subjects. The following provision was followed during the processing and analysis of the childhood cancer incidence data.

i. A cabinet with access limited only to the data users was used to lock up the computer when not in use.
ii. The cancer registry data was treated as strictly confidential.
iii. A password-protected computer with up-to-date antivirus software was used to store and analyze the data.
iv. Any presentation and publication of results will not include specific individual case information identifiable.
v. The principal investigator will destroy the data upon the completion of the study. A dataset without any identifiable data with aggregated information to census tracts will be created and retained for possible future analysis. We will use Autoclave software to destroy the data. Any paper copies or CDs of the data will also be destroyed.

3.3 Methodology Overview

This dissertation consists of three separate studies. Disparity measurement by multiple factors focus three major areas: (a) Measurement of disparity (racial/ethnic and

geographic); (b) Examining the association between risk factors and disparity, and (c) Assessment of spatial access to health care. The first study investigated childhood cancer disparities in the state of Texas based on data from 1995 to 2014 from the perspective of geographic location and race/ethnicity. Two test statistics such as relative (Risk Ratio) and absolute (Risk Difference, R) measures (Goovaerts, Meliker, and Jacquez 2007) were used to calculate the racial disparities across geographic areas. Racial/ethnic disparities of childhood cancer were measured based on Population-weighted RD with strong statistical power and fewer false-positive results.

The second study examined disparities of childhood cancer late-stage diagnosis from the perspective of several social characteristics such as race/ethnicity, socioeconomic status (SES) and geographic location. The study also investigated the role of individual and contextual level variables in these disparities. Spatial access to COGs medical services was calculated using Enhanced 2-step floating catchment area (E2SFCA) method (Luo and Qi 2009). Factorial analysis was performed to identify latent factors responsible for most of the variation among the observed variables. Then, multilevel logistic regression was incorporated to examine how individual and contextual level factors impact the occurrence of childhood cancer late-stage diagnosis by race/ethnicity, socioeconomic status, socio-cultural factor, education, percent African-Americans, spatial access to COGs and rural-urban commuting area and percent health insurance coverage. Geographic disparities of childhood cancer late-stage diagnosis were evaluated using the spatial scan statistics method. This method identifies geographic regions (clusters) with increased risks compared to other regions by implementing tests of significance.

The third study examined the effect of race/ethnicity on overall survival of childhood cancer patients mediated by two mediators. These mediators are spatial accessibility and socioeconomic status. The newly developed causal mediation analysis was used to measure the effect of race/ethnicity on overall survival after blocking and/or operating through mediators. The total effect can be decomposed into natural direct and indirect effects. The study also generated survival curve based on Kaplan-Meier Non-parametric method. The statistically significant survival between two racial groups compared using log-rank test.

4. GEOGRAPHIC VARIATIONS OF RACIAL/ETHNIC DISPARITIES OF CHILDHOOD CANCER IN TEXAS

4.1 Introduction

As of January 2016, more than 15.5 million Americans were living with a history of deadly cancer diseases (American Cancer Society 2018). Most of them were diagnosed with cancer many years ago and currently no evidence of this diseases, whereas some of them diagnosed with cancer recently and still under treatment process. In developed countries, cancer is the second most common cause of death in children (Kaatsch 2010). Although cancer in children represents less than 1% of all new cancer diagnoses, it accounts for considerable death and decreases the span of life. Since 1975 the incidence rate of childhood cancer has slowly increased by 0.6% per year (American Cancer Society 2018). However, there has been a significant improvement in the increase of survival and decrease of mortality.

The overall five year-survival rate now surpasses 80% for children with cancer, and almost 75% of them will live ten years following their diagnosis (Armenian et al. 2013). However, neither all people receive benefit from such progress, nor all people receive equal benefits. Health disparity exists among different population groups of cancer patients based on the cancer control continuum which includes etiology, prevention, detection, diagnosis, treatment, and survivorship. Health disparity research goes back to early 1970s when studies found high mortality rates in African-Americans for certain cancer types compared with their white counterpart (Burbank and Fraumeni 1972; Fontaine et al. 1972).

Cancer disparity research in the academic field was encouraged by the US civil rights movement (Polite et al. 2017). The Surveillance, Epidemiology and End Results (SEER) program was established within the National Cancer Institute (NCI) based on the National Cancer Act of 1971. The SEER program ensures collecting data from a number of population-based registries depending on racial differences in incidence, mortality, and survival.

Numerous studies have already been conducted in racial/ethnic disparities employing cancer continuum as a function of race/ethnicity, and most of which found significant disparity (Pollock et al. 2000; Bhatia et al. 2002; Haimi 2004; Rajput et al. 2014; Zhan and Lin 2014; Grubb et al. 2016). Measurement of disparities should be made in terms of the adverse event which is characterized as undesirable (Keppel et al. 2005). Unlike adult cancer, early diagnosis of childhood cancer is crucial because it allows treatment in the early-stage and resulting in better prognoses for children (Dang-Tan and Franco 2007; Dang-Tan et al. 2008; Stefan and Siemonsma 2011; Ahrensberg et al. 2013; Abdelkhalek et al. 2014). As a matter of fact, it is difficult to diagnose childhood cancer in early-stage because of the rarity of diseases, and misinterpreted and vague symptoms (Cecen et al. 2011; Ahrensberg et al. 2013).

There is a common saying floating around for a long time “early diagnosis is the key” to curing cancer (Halperin and Friedman 1996). The US Department of Health and Human Services announced two overarching goals with the banner of ‘*Healthy People 2020*’ to achieve: (a) health equity and (b) eliminate health disparities (US Department of Health and Human Services 2008). This report revised and reemphasized the definition of

‘health equity’ and ‘health disparity’ because of the slow progress in reducing racial/ethnic and socioeconomic disparity.

The study examined childhood cancer disparities in the state of Texas based on data from 1995 to 2014 from the perspective of geographic location and race/ethnicity. The study also calculated the yearly rate of childhood cancer cases diagnosed at the late-stage for the census tracts those showed significant disparity. This project selected the state of Texas as the study area because of its diverse population group, especially third-largest Hispanic population (Hamilton et al. 2016) which provide a distinct opportunity to study childhood cancer disparities.

The study demonstrates a conceptual framework that outlines a research trajectory from the basic detection of factors contributing to health disparities leading to diseases specific disparity research based on caner control continuum. This framework led our understanding of those factors and help to identify vulnerable population group. The study of childhood cancer disparity from a geographic perspective and the underlying factors will help to identify geographic areas of interest, where elimination of cancer disparity is required. The conceptual framework of this dissertation research is demonstrated in figure 1.1. Factors contributing to health disparities in cancer patients include individual, contextual and medical care factors. Disparities in health must be investigated by casting our spotlight on the determinants of different health outcomes in population level (Whitehead et al. 1992; Warnecke et al. 2008).

The incidence of childhood cancer varies by demographic risk factors such as age, sex and race/ethnicity (Spector et al. 2015). Environmental risk factor such as prior chemotherapy and high dose ionizing radiation is associated with childhood cancer

incidences (Spector et al. 2015). Accurate measurement of environmental exposure is still a major challenge that ultimately limits our understanding of how they impact on childhood cancer risk. Children with certain genetic syndromes (i.e., Down syndrome) and solid organ transplant recipient are at increased risk of leukemia and non-Hodgkin lymphoma respectively (American Cancer Society 2018). Our future study will examine the maternal residential exposure to air toxicant and childhood cancer in offspring.

4.2 Data and Methodology

4.2.1 Study Population

Children cancer incidence data from 2005 to 2014 were obtained from the Texas Cancer Registry (TCR) in the Texas Department of State Health Services (TDSHS). This dataset is only limited to cases of individuals age between 0 to 19 years. Cancer registry dataset usually contains individual level variables which include race/ethnicity, sex, date of birth, year of diagnosis, age at diagnosis, stage at diagnosis, etc. The Surveillance Epidemiology End Result (SEER) program from the National Cancer Institute (NCI) categorized childhood cancer cases at diagnosis into localized, regional and distance. The localized stage was categorized as early stage whereas regional and distant stage was characterized as late-stage based on the clinical and pathological information. Overall, 54.21 percent of cases were diagnosed at the late-stage for all racial groups. We excluded those cases from the study whose stage was unknown or not applicable.

4.2.2 Census demographic data

Census demographic data based on census tracts were collected from the U.S census bureau. Socio-environment data represented by population by age and race/ethnicity were extracted from census 2010 summary file 1 (SF1).

4.2.3 Methodology:

Racial disparities across geographic areas were calculated using two test statistics such as relative (Risk Ratio, RR) and absolute (Risk Difference, RD) measures (Goovaerts, Meliker, and Jacquez 2007). A relative measure compares the rate differences against a reference point whereas an absolute measure calculates a simple arithmetic difference between a target group (African American/Hispanics) and the reference group (non-Hispanic White). The study used population-weighted RD with strong statistical power and fewer false-positive results to measure racial/ethnic disparities of childhood cancer. A positive RD with statistically significant p-value indicated the population group in question had a higher risk than the reference group. The absolute population-weighted risk difference statistic for measuring risk difference ($RD(m_i)$) of late-stage childhood cancer diagnosis in census tract m_i is given in Expression (1)

$$RD(m_i) = \frac{r_1(m_i) - r_2(m_i)}{\sqrt{\bar{r}(m_i)(1-\bar{r}(m_i))\left[\frac{1}{p_1(m_i)} + \frac{1}{p_2(m_i)}\right]}} \quad 4.1$$

Where, $\bar{r}(m_1)$ is the population-weighted average rates of childhood cancer late-stage diagnosis in a census tract. It can be defined as follow (expression 2):

$$\bar{r}(m_i) = \frac{p_1(m_i)r_1(m_i) + p_2(m_i)r_2(m_i)}{p_1(m_i) + p_2(m_i)} \quad 4.2$$

Where, $r_1(m_i)$ and $p_1(m_i)$ represent childhood cancer rate and population size of a target group where as $r_2(m_i)$ and $p_2(m_i)$ represent childhood cancer rate and population size of a reference group in question in this census tract.

The null and alternative hypotheses to test whether the $RD(a_i)$ is statistically significant are as follows (expression 4.3):

$$\begin{matrix} \boldsymbol{H_0}\boldsymbol{:|RD(m_i)|=0} \\ \boldsymbol{H_1}\boldsymbol{:|RD(m_i)|\neq 0} \end{matrix} \quad 4.3$$

Disparities of childhood cancer late-stage diagnosis were identified based on Non-Hispanic whites as a reference. A total of 4,021 (out of 7,416) late-stage children cancer cases were nested within 5,265 census tracts.

The results can be affected by the MAUP (Fotheringham and Wong 1991) and the 'small number' problem. The study interpreted the results cautiously because the 'small number' problem refers to the issue of having small numbers in an area unit when the population size is small, and MAUP may occur when different areal units are used in an analysis.

Following the disparity analysis, the study calculated the rates of late-stage childhood cancer diagnosis in racial groups. Statistically significant and non-significant census tracts were identified from the disparity result. Then, the rate is computed using the number of children cancer cases diagnosed at the late-stage in a specified population group each year, generally expressed as the number of cancer cases per 1,000,000 population at risk.

4.3 Results

4.3.1 Demographic Characteristics

Table 4.1 shows the demographic characteristics of 7700 childhood cancer cases under the age of 19 in Texas from 2005 to 2014. It is apparent from the table that Hispanics constitute the largest population followed by non-Hispanic whites, African-Americans, Asians, and others. The study cohort included 6,899 (89.60%) cases under

the age of 14, and the rest of the adolescents constitute around 10% of the cases. Around 29% of the cases were diagnosed in the early stage whereas 54% of the cases were diagnosed in their late-stage. Based on the last day of follow-up (December 31st, 2014), around 85% of the survived in the state of Texas.

Table 4.1 Basic information on childhood cancer cases in Texas, 2005-2014

Variables	**Number of cases**	**Percentage (%)**
Age Group		
0 - 14	6899	89.60
15 - 19	801	10.40
Race/Ethnicity		
Non-Hispanic whites	3191	41.44
Hispanics	3451	44.82
African-American	775	10.06
Native American	28	0.36
Asian	183	2.38
Others	50	0.65
Unknown	22	0.29
Stage at diagnosis		
Early-stage (*in situ* and local)	2258	29.32
Late-stage (regional and distant)	4161	54.04
Not Applicable/Unknown	1281	16.64
Vital status		
Survived	6560	85.19
Deceased	1140	14.81

4.3.2 Childhood cancer late-stage diagnosis disparity

Racial/ethnic disparities in childhood cancer late-stage diagnosis were calculated using population-weighted risk difference statistics. Racial/ethnic disparities of childhood cancer late-stage diagnosis were presented from geographic perspective. Figure 4.1 shows geographic variation of childhood cancer late-stage diagnosis disparities between Hispanics and non-Hispanic whites based on RD statistics. The study revealed that 47 census tracts (out of 5265) experienced significantly higher late-stage diagnosis rates in

Hispanics. Significant census tracts are dispersedly located outskirt of the metropolitan area, especially the eastern part of Texas. Dallas-Fort Worth metropolitan area had the significant number of census tracts followed by Houston and San Antonio area.

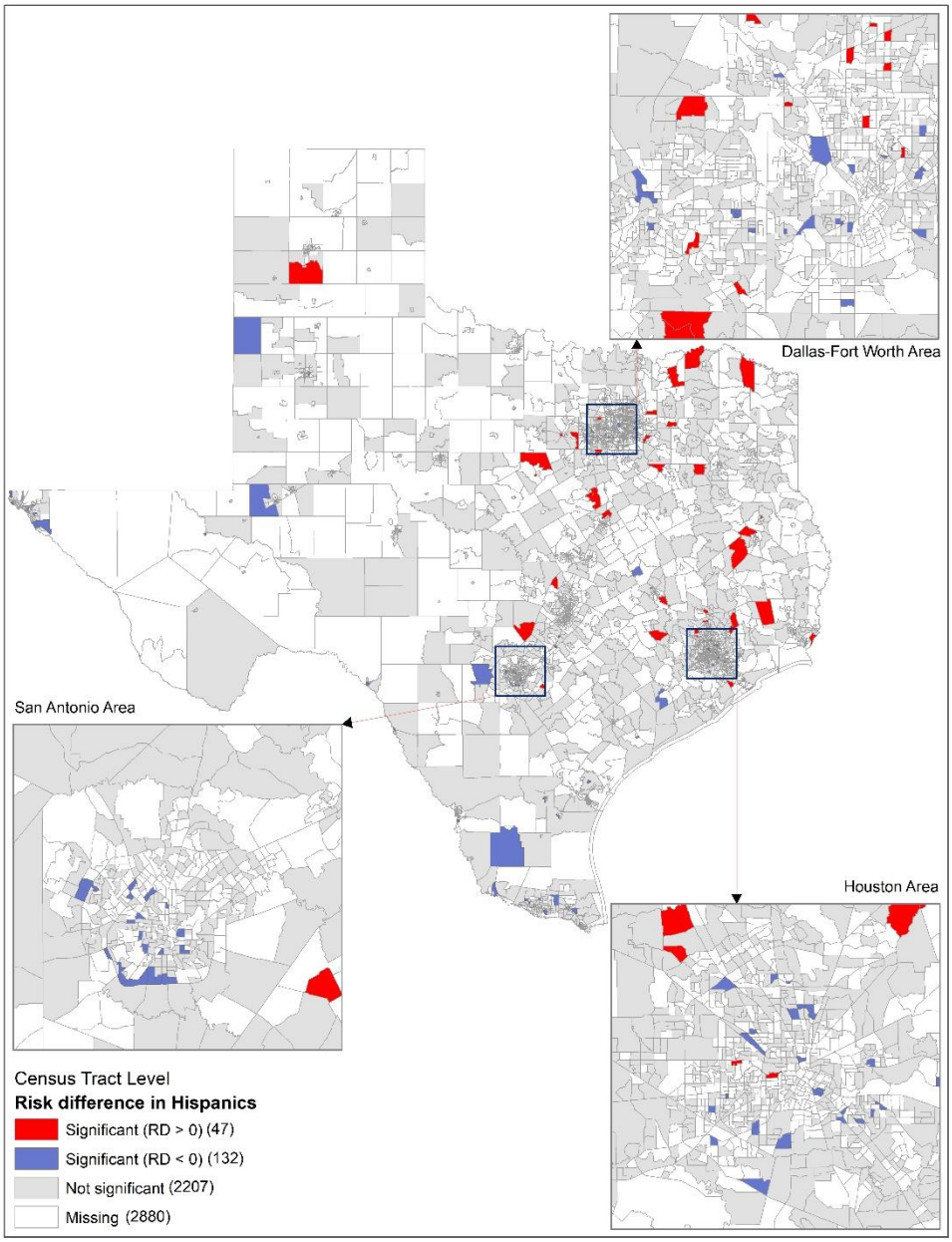

Figure 4.1 Geographic distribution of childhood cancer late-stage diagnosis disparities of Hispanics relative to non-Hispanic white

Likewise, based on RD statistics, Figure 4.2 displays geographic variation of childhood cancer late-stage diagnosis disparities between African-Americans and non-

Hispanic whites. The study found that there were 58 census tracts (out of 5265) those experienced significantly higher late-stage diagnosis rates in African-American (Figure 3). Unlike the geographic disparity of Hispanics, most of the significant census tracts were located inside the metropolitan areas including Houston and Dallas-Fort Worth area. There were few significant census tracts in between Austin and San Antonio area.

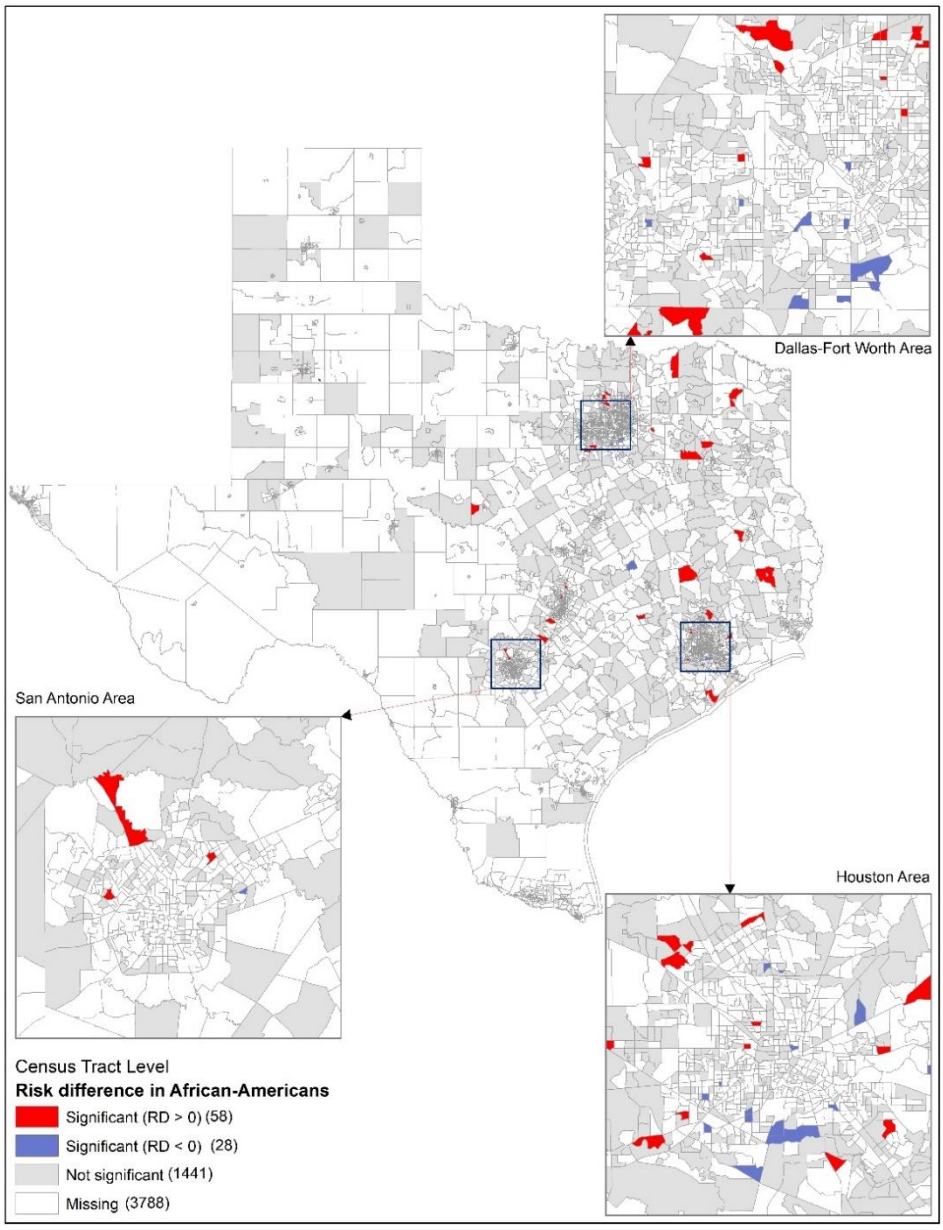

Figure 4.2 Geographic distribution of childhood cancer late-stage diagnosis disparities of African-Americans relative to non-Hispanic white

4.3.3 Childhood cancer rate

The study calculated childhood cancer incidence- and late-stage diagnosis rate for non-Hispanic white, Hispanics and African-Americans combinedly. We employed census 2010 socio-environmental data for rates calculation. Figure 4.3 shows that late-stage diagnosis rate was consistent with incidence rate, meaning childhood cancer diagnosis at late-stage follows a nice pattern relative to the incidence rate for those three racial groups.

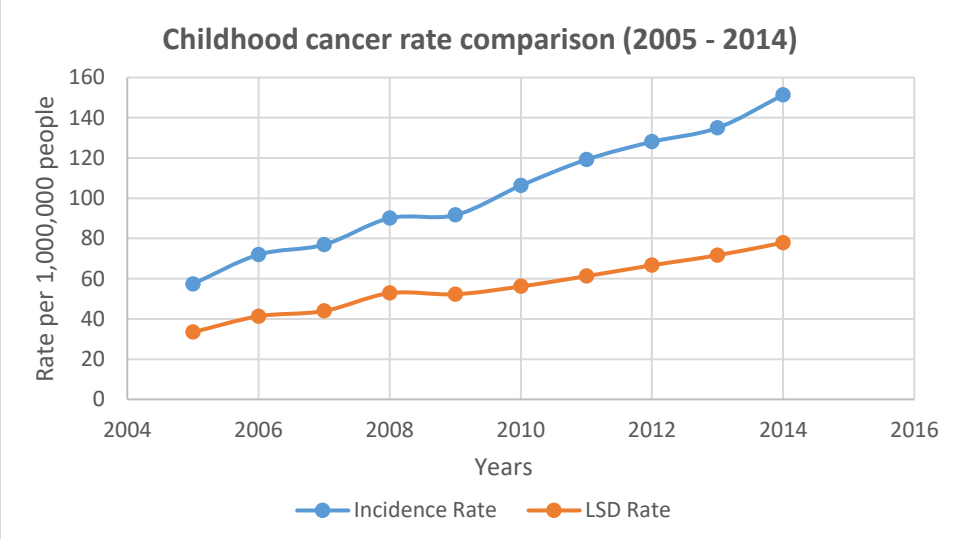

Figure 4.3 Incidence and late-stage diagnosis rate in census tracts with cases for non-Hispanic whites, Hispanics and African-Americans combined

Moreover, children cancer late-stage diagnosis yearly rate was calculated for both African-Americans and Hispanics from the perspective of significant census tracts. The study analyzed the temporal change of childhood cancer late-stage rates from 2005 to 2014. Figure 4.4 shows that there are two visible sharp spikes in 2007 and 2010 (5 % significant level) for African-Americans. In addition, there was a gradual increase in late-stage diagnosis rate till 2010, slowly decrease next few years onward and rise again in 2014 for Hispanics. Our results may seem little different compared with Texas Cancer

Registry because we used census 2010 U.S. standard population age between 0 to 19 years of old for rate calculation.

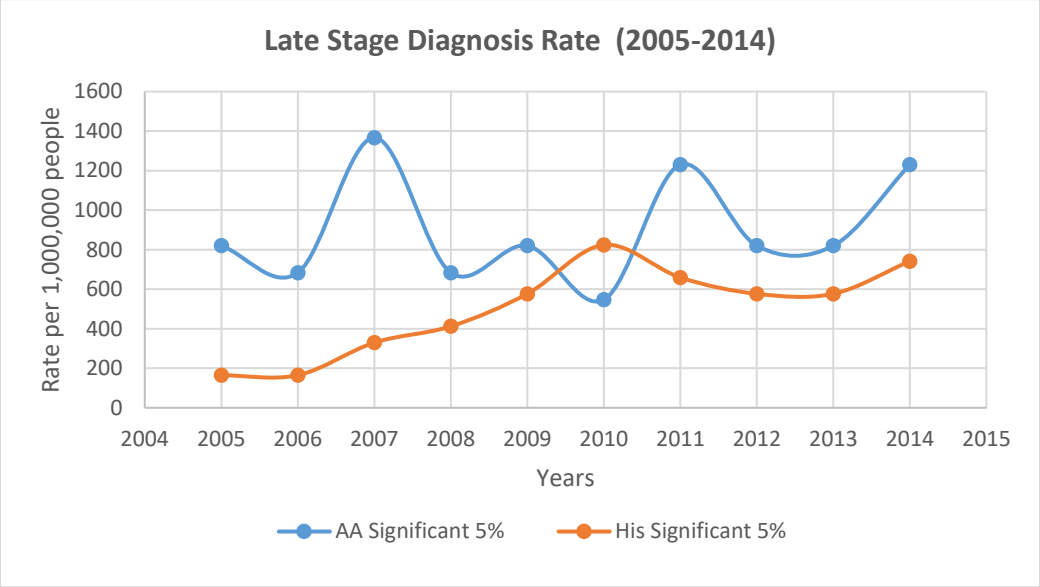

Figure 4.4 Childhood cancer late-stage diagnosis rate of Hispanics and African-Americans in selected census tracts

* Abbreviation: AA, African Americans; His, Hispanics

For both Hispanics and African American children, fewer census tracts showed significant disparity for late-stage diagnosis. It was evident that for both racial groups none of the census tracts overlapped spatially. Although there were fewer African American cases, they showed significant disparity when non-Hispanic white was used as a reference. The yearly late-stage diagnosis rate is high compared with Hispanic children. However, Hispanics displayed relatively better results for significant census tracts count and yearly rates of late-stage childhood cancer diagnosis.

4.4 Discussion:

The study investigated whether the stage of childhood cancer at diagnosis vary by race/ethnicity and geographic location. This project identified significant geographic variation in different racial/ethnic groups in a standard geographic unit. Both African-

Americans and Hispanics showed a significant geographic variation of childhood cancer late-stage diagnosis disparities based on risk difference statistics when compared with non-Hispanic whites as a reference group. The results suggest that African-Americans experienced significant geographic disparity followed by Hispanics. Our findings corroborate with other late-stage studies from the geographic perspective including cervical cancer (Lin and Zhan 2014) and breast cancer studies (Tatalovich et al. 2015; Tian et al. 2012; Kuo, Mobley, and Anselin 2011) in the United States. No reported study before this has examined geographic variation in racial/ethnic disparities in childhood cancer late-stage diagnosis.

The study revealed that although African-Americans had a fewer number of cases diagnosed in their late-stage compared to non-Hispanic whites and Hispanics, a substantial number of census tracts showed significant disparity. African-American children had an elevated risk of late-stage diagnosis compared with their non-Hispanic white counterpart. The childhood cancer yearly rate at late stage diagnosis for African-Americans are also high when compared with their non-Hispanic whites and Hispanic counterpart.

There are a couple of thoughtful insights from various studies. First, Residential isolation of similar racial/ethnic minority group plays an important role in reducing the negative health outcomes, disregarding their economic status (Kuo, Mobley, and Anselin 2011). Second, late-stage diagnosis disparity in eight states suggest that higher rates are predominantly found in an African-American neighborhood where screening facilities are scarce, a lower percentage of a college degree and limited English speaking household (Tatalovich et al. 2015). Third, geographic variation of racial/ethnic disparities in cervical

cancer late-stage diagnosis was further examined accounting for sociodemographic factor, socioeconomic factor, spatial access to health care, health insurance factor, behavioral factor and the percentage of African-Americans (Lin and Zhan 2014). Their study suggests that those factors have a significant impact on the various degree on geographic variation of African-Americans and Hispanics in census tracts.

The findings of this study are restricted to the variability of geographic location and race/ethnicity in relation to stage at diagnosis of children cancer. The study did not take into account the effect of individual-level and contextual-level variables. Next chapter focus on whether socio-economic status, sociocultural and other contextual-level factors were associated with childhood cancer late stage diagnosis. Spatial accessibility may play a very important role in late-stage diagnosis and their preventive care. In addition, there were some census tracts with fewer childhood cancer cases.

There is a number of strengths of this study. First, this is the first attempt to examine the geographic variation of racial/ethnic disparity in childhood cancer late-stage diagnosis in small area unit such as census tracts. Second, the study used 100 % population-based state-wide cancer registry dataset that was well documented and adopted standardized method to categorize stage at diagnosis. The key aspect to contribute our understanding of childhood cancer disparities in two major social domains: geographic location and race/ethnicity.

4.4 Concluding Remarks and Policy Implication

This study identified census tracts with a significant disparity in African-American and Hispanics dispersedly located in the study area, especially the eastern part of Texas. Results from this study suggest that variation in late-stage diagnosis by

geographic location might reflect racial/ethnic diversity, the impact of social differences such as socio-culture, socio-economic, and other pertinent contextual variables. Spatial access to health care services may also have an important effect on the stage at diagnosis. Children are not completely independent; they are dependent on their parents and family for their well-being. Parental literacy and awareness of this deadly disease may save thousands of lives throughout the country.

Childhood cancer intervention programs in targeted regions would reduce disparities in cancer outcomes. Also, the results will contribute to the geographical resource allocation system which in turn help to facilitate preventive health care service and alleviate the diseases burden in children.

5. RACIAL/ETHNIC, SOCIAL CHARACTERISTICS AND GEOGRAPHIC DISPARITES OF CHILDHOOD CANCER IN TEXAS

5.1 Introduction

In the United States, cancer is the second leading cause of death and is a major public health concern. It was estimated that in 2018 alone 1,735,350 cases will be diagnosed which is equivalent to 4,700 new cases each day (Siegel, Miller, and Jemal 2018). Although cancer is not the most common diseases in childhood, it accounts for considerable death in children and decreases the quality and span of life. The survival rate and quality of life have improved for children with cancer in the last few decades, in part because of approximately 70% pediatric cancer patients successfully enroll in clinical trials (Bleyer et al. 1997; Lund et al. 2009). However, neither all people receive benefit from such progress, nor all people receive equal benefits. Health disparity exists among different population groups of cancer patients based on the cancer control continuum which includes cancer etiology, prevention, detection, diagnosis, treatment, and survivorship (Figure1.1).

The principal goal in oncology is the early diagnosis of cancer since it permits an opportunity for timely treatment (Dang-Tan and Franco 2007). The short latency period is an important characteristic of childhood cancers compared with adult cancers, and most often they grow rapidly (Dang-Tan and Franco 2007; Eisenberg et al. 2008; Whitworth, Symanski, and Coker 2008). Childhood cancer diagnosis in its early stage can positively affect on prognosis (Abdelkhalek et al. 2014) and also have an impact on survival which certainly decreases the chance of morbidity (Araz and Guler 2015). There are main three factors that are attributed to delay in diagnosis for childhood cancer,

including patients and/or parent related factor (Abdelkhalek et al. 2014; Dang-Tan et al. 2008; Haimi 2004; Thulesius, Pola, and Hakansson 2000), healthcare facilities (Brown et al. 2009; Dang-Tan et al. 2008, 2010; Haimi 2004), and diseases itself (Dang-Tan and Franco 2007).

The terms ‘patients delay’ and ‘parents delay’ are used interchangeably for diagnosis delay of childhood cancer as children are not able to make their decision for their well-being. In addition to children age and sex, parents’ age (Araz and Guler 2015; Haimi 2004), education level (Abdelkhalek et al. 2014; Ahrensberg et al. 2013; Fajardo-Gutiérrez et al. 2002; Stefan and Siemonsma 2011), socioeconomic status (Abdelkhalek et al. 2014; Araz and Guler 2015) and race/ethnicity (Stefan and Siemonsma 2011; Haimi 2004) are considered as important factors for early stage diagnosis. Health care system-related factors responsible for delayed diagnosis of childhood cancer reported as the access to health care services (Fajardo-Gutiérrez et al. 2002; Wan et al. 2012a) and health professional visits (Dang-Tan et al. 2008, 2010).

Significant research has already been done for race/ethnicity and SES disparities (Krieger 2005; Read and Emerson 2005; Lund et al., 2009; Byers, 2010; Murphy, Tseng, and Shah 2010; Ward et al. 2010 and Borugian et al. 2011; Lin, Schootman, and Zhan 2015). Racial disparities for African-Americans and Hispanic woman were prominent in the case of breast cancer mortality compared to the non-Hispanics white in the case of rate difference measurement (Tian et al. 2010). The study conducted in Egypt found a significant association between SES and childhood cancer delay diagnosis (Abdelkhalek et al. 2014) whereas the study in northern Israel did not find any correlation between SES and delay diagnosis (Haimi 2004).

However, there are several research gaps in the childhood cancer disparities in Texas. First, no study has examined the impact of individual- and contextual-level factors on racial/ethnic and SES disparities of childhood cancer late-stage diagnosis in the US. Second, no reported study has investigated the spatial accessibility to specialized Children Oncology Group (COG) hospitals from the perspective of spatial distribution of demographic in census tracts. The Children Oncology Group (COG) encompasses more than 200 pediatric cancer programs, supported by the National Cancer Institute (NCI), in which health care professional ensure effective treatment while maintaining best cancer research protocol for children (COG 2018; Lund et al. 2009).

This study examined disparities of childhood cancer late-stage diagnosis in Texas based on data between 2005 to 2014 from the perspective of race/ethnicity, geographic location, and various social characteristics. The study investigated the role of individual-level variables (race/ethnicity, age at diagnosis, stage at diagnosis) and contextual level variables (census demographics, socio-environmental (Percent Hispanics and percent African Americans), socio-cultural factor, education-level, spatial access to COGs hospitals, the percentage of health insurance coverage) in these disparities. The findings of this study will contribute to cancer research by investigating the disparities of childhood cancer late-stage diagnosis in the state of Texas.

The study demonstrates a conceptual framework that outlines a research trajectory from the basic detection of factors contributing to health disparities leading to diseases specific disparity research based on cancer control continuum (Figure 1.1).

There are a number of ways to measure racial/ethnic disparities (Chu, Miller, and Springfield 2007; Keppel et al. 2005). The most conventional way to quantify the excess

cancer burden of racial/ethnic group is to compare with a reference group. The same principle applies to the racial/ethnic disparities of childhood cancer incidence, late-stage diagnosis, and mortality. The study of childhood cancer disparity from a geographic perspective and the underlying factors will help in identifying geographic areas of interest, where elimination of cancer disparity is required.

5.2 Data and Methodology

5.2.1 Study Population

The study used statewide childhood cancer data from the Texas Cancer Registry (TCR) in the Texas Department of State Health Services (TDSHS). There were 7,700 childhood cancer incidences in the state of Texas from 2005 to 2014. The dataset only limited to cases of individuals age between 0 to 19 years. The Institutional Review Boards (IRB) of the Texas Department of State Health Service and Texas State University approved the study protocol of this study and the use of the data.

5.2.2 Study Variables

This study included mutually exclusive racial group: Non-Hispanic white, Hispanics and African-Americans because of the small proportion (3.69%) of the reported cases for Native Americans, Asians, and other racial groups. Race/ethnicity, age at diagnosis, stage at diagnosis and tumor grade were listed as individual-level variables. Surveillance Epidemiology End Result (SEER) program from the National Cancer Institute (NCI) categorized childhood cancer cases at diagnosis into localized, regional and distant stage. The relative proportion of the *in situ* and localized, regional, distant, and not applicable or unstaged was 2157 (29%), 835 (11%), 3177 (43%), and 1232 (17 %) respectively. Cases with not applicable and unknown stage were excluded from the

study. Based on the clinical and pathological information, *in situ* and localized stage was categorized as early stage whereas regional and distant stage was characterized as late-stage.

The study used the American Community Survey (ACS) 5-year estimates (2006-2010) for census tracts in the state of Texas. The ACS is a continuing national survey that generates period estimates of demographic, housing, and socioeconomic characteristics of the U.S population. There are three primary uses of ACS estimates including (a) understanding the demographic characteristics of an area for local planning purposes, (b) comparing across areas, and (c) measure the change over time. It is recommended to use 5-year estimated for the small geographic area (less than 20,000 population) (US Census Bureau 2008).

This study also used contextual variables which include census demographic, socio-environmental (Percent Hispanics and percent African Americans), spatial access to COGs hospitals, percentage of health insurance coverage in census tracts level. There were 10 census tract level demographic variables from ACS 2010 dataset: percent below poverty, percent unemployed, median household income, median home value, percent without high-school degree, percent without college degree, percent limited English speaking household, female household children under 18 years of age, average family size, percent foreign-born under 18 years of age, percent household without a car. Socio-environmental variables such as children by age and race/ethnicity, percentage of African-Americans, percentage of Hispanics were extracted from census 2010 summary file 1 (SF1). These variables were used for cancer disparity research, and they fall under the broad umbrella of socio-environmental, socio-cultural and socio-economic domains.

Urbanization was calculated using ten primary RUCA (Rural-Urban Commuting Area) code based on 2006-2010 ACS and 2010 decennial census tracts. The study delineated four major areas in census tracts level including metropolitan, micropolitan, small town and rural commuting area.

5.2.3 Methodology:

Relative Spatial access to Children Oncology Groups (COG) medical services were calculated using enhanced 2-step floating catchment area (E2SFCA) method (Luo and Qi 2009), which is an updated version of basic gravity-based spatial access model by (Hansen 1959; Joseph & Bantock, 1982). The E2SFCA method first calculates a spatial access index (SPAI) for each census tract and the level of relative spatial access of the entire region is then computed using a ratio of SPAI in each census tract to the average SPAI. The measurement of supply-to-demand ratio, Rj in census tracts of j is as follow:

$$R_j = \frac{S_j}{\sum_{j\in\left(d_{kj}\in D_t\right)} P_k W_r} \quad 5.1$$

Where S_j denotes the health care capacities of at location j, P_k represents the population size of any census track k, D_t represents the subzones of catchment in terms of time intervals, and W_r denotes the impedance weight for D_t based on the Gaussian function ($W_r = f(d_t)$) (Luo and Qi 2009). The SPAI of each area unit i (A_i^F) is to be calculated using the following steps of

E2SFCA:

$$A_i^F = \sum_{I\in\{d_{il}\in D_t\}} R_i W_r \quad 5.2$$

Where R_i denotes the supply-to-demand ratio for any health care service location I inside the catchment and d_{il} represents the travel cost between I and i. The study used travel

time as the network travel impedance/cost with focal catchment area (FCA) dimension of 300 minutes. The COG health care service locations represent the service supply point location and the total number of populations under the age of 19 represents the service demand in census tracts.

Factor analysis was performed to analyze the covariation among the observed variables and reduce the dimension of census demographic variables. This method helps to identify a number of latent factors accounted for most of the variation among the observed variables. Exploratory factor analysis also lists variables appears to define each factor and then helps to label them. This method employed the function factanal () with a varimax rotation that uses 'maximum likelihood' function as opposed to 'principal component' to derive the factors (Thomas 2014). When maximum likelihood function was used, there exists a (conservative) significance test for the null hypothesis that the extracted factors are sufficient. Varimax rotation basically orthogonally turns the factor axes with the objective of amplifying the difference of the squared loadings of a factor on every one of the variables in the factor matrix. For this reason, interpretation of a factor much simpler because each variable tends to load more heavily on a single factor while load significantly lower on other factors. The method also reports the sums of squared (SS) loadings (eigenvalues) or proportional variance in all variables which is accounted for by that factors.

The high eigenvalue in a factor help explaining the variance in the variables. If the eigenvalue is greater than 1 for a factor, is useful/important based on the Kaiser rule (Kaiser 1960). Internal consistency reliability was measured using an alpha function with two estimates: Cronbach's coefficient $\boldsymbol{\alpha}$ (Cronbach 1951) and Guttman's λ_6 (G6)

(Guttman 1945). Both of these measures are positive functions of the number of variables in a test and represents the average inter-collinearity and reliability of the variables in the test.

Multilevel logistic regression was used to analyze how individual and contextual level factors impact the occurrence of childhood cancer by race/ethnicity and social domains. A mixed effects logistic regression in R 3.5.1 (R Core Team 2018) package 'glmer' (Generalized Linear Mixed-Effects Models) was employed to model binary outcome variables (Agresti 2013; Bruin 2006). The relationship of several predictor variables (x_1, x_2 ,x_3,….. x_k) to a dichotomous dependent variable (γ) can be described using a mathematical model called logistic regression. Here Y is typically coded as 1 (significant) or 0 (not-significant) for its two possible categories (Kleinbaum et al. 2008; Tian, Wilson, and Zhan 2011). Hierarchical or clustered data at different level (i.e., patient-level and census track-level) were analyzed using multilevel regression model, taking account of the variability associated with each level of the hierarchy. This model can be applied to data with binary outcome variable (Dai, Li, and Rocke 2006).

$$Y_{ij} = \pi_{ij} + e_{ij} \qquad 5.3$$

$$\text{Logit } (\pi_{ij})A = log\frac{\pi_{ij}}{1-\pi_{ij}} = \alpha_j + \beta X_{ij} \qquad 5.4$$

$$\alpha_j = \alpha + u_j \qquad 5.5$$

Where Y is a binary outcome variable, i is the patient level indicator, j is the census tract level indicator, π_{ij} is the probability of the late-stage diagnosis for patient i in the census-track j, and e_{ij} is patient level random error. The logit function assumes that each census tract has its own intercept α_j measures census tract level effects. α_j is a linear

combination of a grand mean α and a deviation u_j from that mean. Therefore, the hierarchical model has both fixed effect (α, β) and random effects u_j.

We used three separate models to measure late-stage diagnosis disparity for both race/ethnicity and SES. In the case of childhood cancer late diagnosis disparity by race/ethnicity, the first model (Model I) included age group and race/ethnicity as the independent variable. The second model (Model II) included age group, race/ethnicity, and SES. The third model (Model III) examined the impact of contextual variables by including independent variables in Model II along with contextual factors, including socio-cultural factor, education level, percent African-Americans, spatial access to COG hospitals, and percent health insurance coverage. Likewise, to measure the late-stage diagnosis disparity by SES, the first model (Model I) included age group and SES. The second model (Model II) include an independent variable in Model I and race/ethnicity. The third model (Model III) included the contextual factors mentioned above along with variables in model II.

The study used spatial scan statistics (Kulldorff 1997) to measure the geographic disparities of childhood cancer late-stage diagnosis. The scan statistics employed discrete poisson model assuming that the number of childhood cancer cases diagnosed in the late-stage followed a poisson distribution. It is also inferred that if there are no covariates, the number of cases is proportional to the risk population. Spatial scan statistics identify most likely cluster and secondary cluster using maximum likelihood estimation and also evaluate their significance based on 9999 Monte Carlo simulations (Kulldorff 1997). The analysis was performed in the SaTScan (version v9.4.4) software (Kulldorff and Information Management Services Inc. 2018).

5.3 Results:

Figure 5.1 shows heterogeneous spatial access to Children Oncology Group hospitals in Texas. COGs hospitals are located in urban areas where most of the population clustered. Based on the accessibility results, urban areas with high-density population has high accessibility or easy access to COG services compared to their rural counterpart (especially, Upper East, Southeast, the tip of high plains, part of northwest and west of Texas to all the way Upper Rio Grande areas are less accessible to specialized COGs hospitals. Hospital locations stretch from the Gulf area to along the interstate highway I35 corridor to Dallas metropolitan area showed high accessibility depending on the population distribution and their closeness to the hospitals.

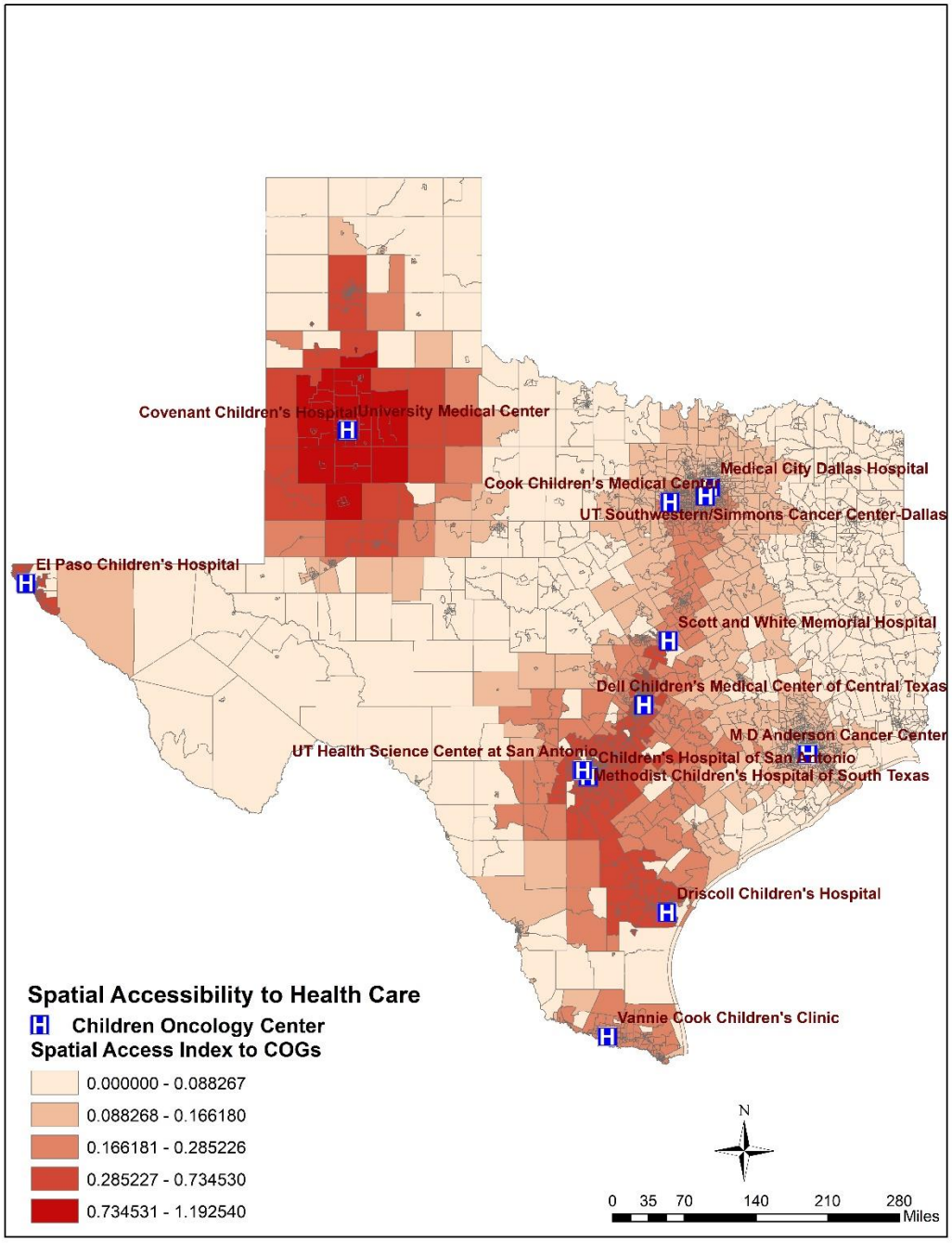

Figure 5.1 Spatial access to Children Oncology Group (COG) services

(Note: Values close to 1 or higher represents high accessibility)

Factor analysis extracted four factors including Socioeconomic Status (SES), Socio-cultural, Educational status, and percent African-Americans. Although in the literature educational status falls under SES, but percent without high school and college

degree loaded independently with high factor loadings. Percent African-Americans also had a significantly high SS loading and considered as an independent factor. Table 5.1 shows all four-factor had high eigenvalue (>1.00), and relative cumulative variance. The standard alpha and Guttman's λ_6 (G6) were 0.84 and 0.89 respectively which means variables are highly correlated to each other. Although Cronbach's **α** is a popular measure, it overestimates the first factor saturation and underestimates the reliability of a test (Revelle 2018).

Table 5.1 Factor loadings and the percentage of cumulative variance explained by each factor

Variables	**Factors**			
	Socioeconomic status	**Socio-cultural factor**	**Education level**	**Percent of African Americans**
Percent below poverty	**0.761**	0.376	0.212	0.106
Percent Unemployed	0.463	0.165	0.211	0.288
Median household Income	-0.588	-0.176		
Median home value	0.316		0.218	
Percent without a high-school degree		0.129	**-0.921**	-0.102
Percent without college degree	0.365	0.315	**0.823**	
Percent Limited English-speaking household	0.438	**0.739**		-0.109
Female household children under 18 years of age	0.404	0.420	0.264	0.435
Average family size	0.130	**0.791**	0.238	
Percent foreign-born under 18 years of age	0.190	0.349	-0.159	
Percent household without a car	**0. 738**	0.112		0.217
Percent Hispanics	0.336	**0.799**	0.221	-0.204
Percent African-Americans	0.188			**0.928**
Eigenvalue (SS loadings)	2.483	2.467	1.886	1.283
Cumulative variance	0.177	0.354	0.488	0.580

Chi-squared test of independence of the factor was performed to see if there is a significant difference between early-stage and late-stage diagnosed groups in terms of individual and contextual factors. There was a statistically significant difference between early- and late-stage diagnosis cases concerning individual-level characteristic including race/ethnicity, and contextual-level characteristic including SES, Sociocultural, spatial access to COGs and percent of health insurance coverage. Table 5.2 shows that Hispanic children with cancer diagnosed at late-stage constitute around 49 percent alone compared with non-Hispanic white and African-Americans counterparts. The proportions of late-stage diagnosis cases are significantly high for all three races except for Hispanics, whom scored more than double. In addition, a large proportion of cases diagnosed at their younger ages as low as 14 compared with 15 -19 years of old. There were 91.05 percent cases diagnosed at late-stage under the age of fourteen.

Table 5.2 revealed that socioeconomically advantaged group more likely to diagnosed at early-stage. Among the late-stage cases, there was a gradual increase of late-stage diagnosis cases in the socioeconomically disadvantaged groups. There was a gradual increase of cases diagnosed at late-stage in terms of decrease in accessibility to COGs with the exception in most deprived areas (22%). The percentage of early- and late-stage diagnosis cases increased gradually with the decrease of health insurance coverage in the census tracts.

Table 5.2 Selected characteristics of childhood cancer stage at diagnosis in Texas 2005 to 2014 in term of individual and contextual-level factors.

Selected Characteristics	Early Stage (n = 2,163)		Late Stage (n = 4,021)	
	Cases	%	Cases	%
Age Group				
0 - 14	1,936	89.51	3,661	91.05
15 - 19	227	10.49	360	8.95
Race/Ethnicity*				
Non-Hispanic White	984	45.49	1,639	40.76
Hispanics	927	42.86	1,992	49.54
African-Americans	252	11.65	390	9.70
Socioeconomic status*				
1st quartile (High)	676	31.25	1175	29.22
2nd quartile	551	25.47	904	22.48
3rd quartile	455	21.04	907	22.56
4th quartile (Low)	481	22.24	1035	25.74
Socio-cultural factor*				
1st quartile (High)	388	17.94	647	16.09
2nd quartile	469	21.68	871	21.66
3rd quartile	629	29.08	1091	27.13
4th quartile (Low)	677	31.30	1412	35.12
Education				
1st quartile (High)	551	25.47	938	23.33
2nd quartile	544	25.15	1127	28.03
3rd quartile	618	28.57	1119	27.83
4th quartile (Low)	450	20.80	837	20.81
Percentage of African-Americans				
1st quartile (High)	487	22.52	994	24.72
2nd quartile	521	24.08	975	24.25
3rd quartile	607	28.06	1053	26.19
4th quartile (Low)	548	25.34	999	24.84
Spatial Access to COG*				
1st quartile (High)	542	25.06	989	24.59
2nd quartile	563	26.03	1008	25.07
3rd quartile	532	24.60	1129	28.08
4th quartile (Low)	526	24.31	895	22.26
Percentage of Health Insurance Coverage*				
1st quartile (High)	532	24.60	872	21.69
2nd quartile	507	23.44	902	22.43
3rd quartile	540	24.96	1031	25.64
4th quartile (Low)	584	27.00	1216	30.24

*Chi-squared test of independence of the factors between early and late-stage diagnosed groups were significant ($P < 0.05$)

Table 5.3 reveals statistically significant race/ethnicity disparities of childhood cancer late-stage diagnosis. Compared with non-Hispanics white cases, Hispanics had an elevated risk of diagnosis at advanced stage (Odd Ratio [OR], 1.25; 95% CI, (1.09 – 1.43) after adjusting for both individual and contextual variables. African-American had a lower risk of diagnosis at late-stage compared with their white counterpart (OR, 0.92; 95% CI, (0.75 – 1.13) after adjusting for both individual and contextual covariates. The possible reason for that may be very few numbers of African-American cases, and forty percent of them diagnosed at the early stage. It is apparent from Table 5.3 that there is a significant inverse relationship between childhood cancer diagnosis at the late-stage and SES status in the census tracts. Census tract with lowest SES had an elevated risk of late-stage diagnosis (OR, 1.23; 95% CI, (1.06 – 1.42) after adjusting for age group, which means lowest SES were 23 percent more likely to be diagnosed at an advanced stage. Model III reveals that the chance of census tracts with the lowest SES to be diagnosed 11 percent more after adjusting for individual and contextual covariates, compared with their socioeconomically advantaged group.

Socio-cultural factor showed higher elevated risk for late-stage diagnosis when they were fitted alone in the logistic regression (model I), especially for lower socio-cultural factor (OR = 1.25; 95% CI =1.07 - 1.47), and the risk decreased slightly after adjusting for other factors. The 2nd quartile of parental education level showed a significantly higher risk for late-stage diagnosis in all three-case scenario (with or without other variables). Although the risk was comparatively lower in third quartiles and again pick-up in the 4th quartiles (OR = 1.09, 1.14 and 1.23 respectively, 95% CI). Percent African-American did not show significant affect on stage at diagnosis.

Compared with a census tract with the highest accessibility, a census with the lower accessibility to COGs was more likely to have a significantly higher late-stage diagnosis after adjusting for covariates (OR = 1.26; 95% CI = 1.07-1.48), and the risk decreases sharply for census tracts with lowest spatial access. The study revealed that the micropolitan area has a higher risk of late-stage diagnosis after adjusting for covariates (1.18; 95%CI = 0.95 -1.45) when compared with the large metropolitan area. It was apparent that rural area has a slightly higher risk than small town after adjusted for other variables (1.08; 95%CI = 0.68-1.70). Percent health insurance coverage showed significant affect on stage at diagnosis, especially census tract with the lowest percentile are more likely to have a higher late-stage diagnosis (OR = 1.26; 95%CI = 0.97 – 1.63).

Table 5.3 Odds ratio of childhood cancer late-stage diagnosis by race/ethnicity and other social domains

Variables	Odds ratio of Model I (95% CI)	Odds ratio of Model II (95% CI)	Odds ratio of Model III (95% CI)
Race/Ethnicity			
Non-Hispanic White	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Hispanics	1.28 (1.15 - 1.44)**	1.25 (1.11 - 1.40)**	1.25 (1.09 - 1.43)**
African-Americans	0.93(0.78 - 1.11)	0.90 (0.75 - 1.08	0.92 (0.75 - 1.13)
Socioeconomic status			
1st quartile (High)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
2nd quartile	0.94 (0.82 - 1.09)	0.94 (0.81 - 1.08)	0.92 (0.79 - 1.07)
3rd quartile	1.15 (0.99 - 1.33)	1.11 (0.96 - 1.29)	1.09 (0.93 - 1.29)
4th quartile (Low)	1.23 (1.06 - 1.42)**	1.14 (0.98 - 1.33)	1.11 (0.92 - 1.33)
Socio-cultural factor			
1st quartile (High)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
2nd quartile	1.12 (0.94- 1.32)	1.10 (0.93 - 1.31)	1.10 (0.91 - 1.32)
3rd quartile	1.04 (0.89 - 1.22)	0.98 (0.84 - 1.16)	0.98 (0.82 - 1.18)
4th quartile (Low)	1.25 (1.07 - 1.47)**	1.09 (0.91 - 1.29)	1.03 (0.83 - 1.27)
Education			
1st quartile (High)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
2nd quartile	1.22 (1.05 - 1.42)*	1.19 (1.02 - 1.38)*	1.21 (1.03 - 1.42)*
3rd quartile	1.06 (0.92 - 1.23)	1.05 (0.91 - 1.21)	1.08 (0.92 - 1.27)
4th quartile (Low)	1.09 (0.93 - 1.27)	1.14 (0.98 - 1.34)	1.23 (1.02 - 1.48)*
Percent African-Americans			
1st quartile (High)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
2nd quartile	0.92 (0.79 - 1.07)	0.97 (0.83 - 1.13)	0.96 (0.82 - 1.14)
3rd quartile	0.85 (0.74 - 0.99)*	0.91 (0.78 - 1.06)	0.90 (0.76 - 1.07)
4th quartile (Low)	0.89 (0.77 - 1.04)	0.96 (0.82 - 1.13)	0.95 (0.80 - 1.13)
Spatial Access to COGs			
1st quartile (High)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
2nd quartile	0.97 (0.84 - 1.13)	0.99 (0.86 - 1.15)	0.99 (0.84 - 1.16)
3rd quartile	1.18 (1.01 -1.37)*	1.24 (1.07 - 1.45)**	1.26 (1.07 - 1.48)**
4th quartile (Low)	0.93 (0.80 - 1.08)	1.00 (0.86 - 1.17)	1.00 (0.85 - 1.17)
Rural-Urban Commuting Area			
Metropolitan	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Micropolitan	1.15 (0.93 -1.40)	1.16 (0.95 - 1.43)	1.18 (0.95 -1.45)
Small Town	1.03 (0.77 - 1.40)	1.05 (0.78 - 1.41)	1.07 (0.78 - 1.46)
Rural	0.96 (0.62 - 1.51)	1.03 (0.66 - 1.62)	1.08 (0.68 - 1.70)
Percent Health Insurance Coverage			
1st quartile (High)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
2nd quartile	1.03 (0.89 - 1.20)	1.01 (0.87 - 1.17)	1.08 (0.91 - 1.29)
3rd quartile	1.18 (1.01 - 1.37)*	1.11 (0.95 - 1.30)	1.21 (0.99 - 1.48)
4th quartile (Low)	1.28 (1.10 - 1.49)**	1.15 (0.97 - 1.36)	1.26 (0.97 - 1.63)

**p<0.005 & *p<0.05

Model I is adjusted for age and race/ethnicity. Model II is adjusted for age and race/ethnicity, and SES. Model III is adjusted for all factors of Model II, with the addition of contextual factors, including socio-cultural factors, education-level factor, percentage of African Americans, percentage of health insurance coverage, and spatial access to Children Oncology Center.

Spatial scan statistics identified six clusters mostly located in metropolitan areas for childhood cancer late-stage diagnosis. None of the clusters came out to be statistically significant. There were three clusters in the Houston, two in Dallas-Fort Worth and last one in the San Antonio area.

5.4 Discussion:

Access to health care services is an important criterion for human well-being. The geographical distribution of the availability of health care services (supply) and peoples' residence addresses (demand) is not uniform. As a result, spatial access to health care services varies across spaces (Luo and Wang 2003). The spatial accessibility research based on primary health care locations already been done for various elder cancer types including breast cancer (Tian et al. 2012) colorectal cancer (Wan et al. 2012b), cervical cancer (Lin et al. 2015). Cancer in children is rare and identifying the symptoms are even harder for medical practitioners. Therefore, childhood cancer patients need specialized care and treatment from COG experts.

The Children Oncology Group (COG) experts provide their services in particular cancer hospitals, children's hospitals and university medical centers in the US, Canada and a growing number of locations internationally. The principal goal of the Children Oncology Group (COG) is the inclusion of proportional racial/ethnic groups diagnosed with cancer in clinical trials. There are only fifteen COG sites in Texas, mostly clustered in the urban area (COG 2018). Texas is the second largest state in the US, and the population distribution and their living environment (rural and urban) also varies across space.

This study revealed that most of the rural area in Texas is highly inaccessible to COG services which alleviate the quality and span of life of children with cancer (Figure 5.1). Micropolitan areas are more likely to have a higher risk of late-stage diagnosis compared with the large metropolitan area after adjusting for covariates. However, small town and rural areas also displayed certain risks for late stage diagnosis. No reported study before this one has examined the role of spatial access to COG in childhood cancer stage at diagnosis.

The study found significant racial/ethnic and SES disparities in late-stage diagnosis of childhood cancer. We used three different models to examine childhood cancer late-stage diagnosis by race/ethnicity and SES. The study revealed a significant disparity for Hispanics compared with white counterpart after adjusting for age, race/ethnicity, SES and contextual factors. Hispanic children were more likely to present with an advanced stage which corroborates with two other studies for childhood melanoma in Texas (Hamilton et al. 2016) and New Mexico (Rajput et al. 2014). Also, several other studies found significant disparities in late-stage diagnosis for Hispanics and African Americans (Lin et al. 2015; Tian et al. 2012; Wan et al. 2013; Ward et al. 2010). After adjusting for both individual and contextual covariates, African-American showed a lower risk of diagnosis at late-stage compared with their white counterpart. One of the important reasons might be insignificant case number and most of which diagnosed in the early stage.

The difference in SES status known to impact cancer outcomes. In this study, SES was constructed based on multiple indicators such as percent below poverty, percent unemployed, median household income, and percent household without a car. This

important indicator has not been examined enough for childhood cancer patients. In a few studies, SES was not found significantly associated with delay diagnosis (Dang-Tan et al. 2010; Haimi 2004; Martin et al. 2007) and showing no indication of increasing the risk of childhood cancer (Marquant et al. 2016).

Childhood cancer stage at diagnosis was found strongly correlated with SES. The relative proportion of cases for both early and late-stage at diagnosis in the socioeconomically advantaged group were high. However, there was an inverse relationship with the increase of social deprivation which means the increase of late-stage cases with a decrease of early-stage childhood cancer patients. Results from this study suggested that there were significant contextual SES disparities among childhood cancer late-stage diagnosis which is consistent with previous disparity research (Araz and Guler 2015; Fajardo-Gutiérrez et al. 2002; Tian et al. 2012; Wan et al. 2013).

Parental education level was found to be an important predictor for childhood cancer late-stage diagnosis. Census tract with lower parental education level showed higher late-stage diagnosis risk as education level is closely associated with socioeconomic status. Education level can be used as a proxy for SES status because it remains fairly stable through adulthood whereas the change in health status is less affected compared with occupational status and income (Krieger, Williams, and Moss 1997). A retrospective study of Egyptian children found that the education level of parents was statistically significant with a total delay diagnosis (Abdelkhalek et al. 2014). Moreover, two other studies in Mexico concluded that parental lower education level as an important factor for children diagnosed in advanced stage (Fajardo-Gutiérrez et al. 2002; Ramírez-Ortiz et al. 2014).

The study found an elevated risk of late-stage diagnosis for socio-culturally disadvantaged groups in a census tract. The study also reported a significant difference in selected characteristics of childhood cancer stage at diagnosis and socio-cultural factor. The number of cases increased steadily for both early- and late-stage diagnosis in terms of socio-culturally disadvantaged groups which is similar to cervical cancer (Zhan and Lin 2014) and colorectal cancer (Henry, Sherman, and Roche 2009) disparities in Texas and New Jersey respectively. It is worth noting that percent limited English speaking household, average family size, and percent Hispanics loaded heavily in sociocultural factor, which is convincing based on the sociodemographic characteristics of Texas. The sociocultural factor may limit the ability to navigate the medical system, knowledge about health literacy and communication with health professionals (Henry et al. 2009).

Finally, a census tract with the lowest percentage of health insurance coverage is more likely to show a significantly higher risk of childhood cancer late-stage diagnosis when compared with the highest percentage of children have health insurance in a census tract. This study also revealed significant difference for cases diagnosed in both early- and late-stage diagnosis; the number of late-stage diagnosis cases was more than doubled in the census tracts with the lowest percentage of health insurance coverage. It is also noted that the relatively high proportion of late-stage cases decrease with the increase of health insurance enrollment and vice-versa for early stage. Lack of sufficient health insurance coverage can pose a major obstacle to adequate treatment and preventive healthcare services, more importantly adversely affect the incidence and mortality throughout the cancer control continuum which extends from etiology, prevention, detection, diagnosis, treatment, and survival to palliative care (Ward et al. 2008).

This study has several limitations to be noted when interpreting the results. First, 13 (0.17% of the total cases) childhood cancer cases were excluded from the analysis because of inadequate data. Also, we had to exclude 1232 (16.61 % of total cases) cases from the logistic regression equation due to not applicable/unknown Stage at diagnosis. Furthermore, tumor grade was excluded for this study because grade descriptions were unknown (not stated, or not applicable) for more than 50% cases. Second, while processing a sociodemographic dataset, we had to compromise 46 census tracts records (0.87% of the total) because of the lack of information. Third, in the accessibility analysis, we assumed that the population lives in the centroid of each census tracts, that is acceptable for census tracts with small area boundary. However, in the real world the distribution of shape and size of the census tracts, and the number of the population varies in time and space. Fourth, the study also considered each Children Oncology Group (COG) center provide equal services in terms of medical professionals and logistics which is unrealistic and calls for further investigation.

5.5 Concluding Remarks and Policy Implication

Factor associated with childhood cancer stage at diagnosis plays an important role in disease prognosis and their well-being. Identifying those factors are a challenging task for any disparity research, especially for spatial epidemiology. This study presents a comprehensive examination of childhood cancer late-stage diagnosis disparities in terms of individual and contextual-level factors. Results from these selected characteristics of childhood cancer stage at diagnosis will be useful for childhood cancer intervention program. It will contribute to the process of long-term policy making to eliminate the racial/ethnic and SES disparities in a microscale basis.

Spatial accessibility to COGs healthcare services at this fine spatial resolution is the first attempt in the United States for an analysis of this nature. The study found significant discrepancies in healthcare accessibility for rural and urban settings. Resource should be allocated in the targeted socioeconomically disadvantaged areas with a high percentage of linguistically isolated household, household without a car, and above all areas with highly dense Hispanics and African-Americans population. Future work should explore how racial/ethnic disparities changes over geographic space in finer geographic scale. It is also recommended to investigate geographic cluster of the childhood cancer late-stage diagnosis.

6. CAUSAL MEDIATION ANALYSIS FOR CHILDHOOD CANCER SURVIVAL INVESTIGATION

6.1 Introduction

Over the past 50 years, childhood cancer survival has significantly improved because of the advancement in medical science (Ness et al., 2015). A growing number of cancer patients now enjoys cancer survivorship because of continuous improvement in treatment, therapy, and overall supportive care. It was reported that 5-year survival rates for all cancer types had increased significantly from 58% during the mid-1970s to 83% during 2007 to 2013 for children and 68% to 84% for adolescents (Siegel, Miller, & Jemal, 2018). However, neither all segments of the U.S population receive benefit from such progress, nor all people receive equal benefits.

In the United States, the current 5-year relative survival rate is 61 % in African-American and 68 % in whites for all cancers combined (Howlader et al., 2016; Siegel et al., 2018). The disparity in health exists among different population groups of cancer patients based on the cancer control continuum which includes cancer etiology, prevention, detection, diagnosis, treatment, and overall survivorship. The US Department of Health and Human Services announced four overarching goals with the banner of '*Healthy People 2020*' to achieve; the second goal pointed out the importance of 'Achieving Health Equity and Eliminating Health Disparities' (US Department of Health and Human Services, 2008). Elimination of disparities can only be assured through the improvement in survival and reduction in cancer mortality among disadvantaged groups (Bhatia, 2011). Geographic locations, race/ethnicity, sex, age group, and socioeconomic

status are common indicators of disparities in childhood cancer (Holmes, Vandenberg, McClarinl, & Dabney, 2015; Schottenfeld & Fraumeni, 2006).

Significant research has already been done for racial/ethnic disparities of childhood cancer survival (Bhatia et al., 2002; Kadan-Lottick, Ness, Bhatia, & Gurney, 2003; Linabery & Ross, 2008; Park et al., 2005). African-Americans and Hispanics had lower survival rates in most cases compared with their Non-Hispanic white counterpart. Socioeconomic status (SES) is known to impact cancer outcome, constructed based on multiple indicators. In addition to SES, contextual variable such as spatial accessibility is also considered as an important factor for childhood cancer treatment and their overall outcome. Childhood cancer patients require specialized treatment facilities with multidisciplinary care only dedicated to pediatric services (Fluchel et al., 2014). Children Oncology Group (COG) hospitals facilitate those services in their specialized centers ensuring equal representation of racial/ethnic groups in a clinical trial (Lund et al., 2009). Unfortunately, most of the COG centers tend to be located in large urban areas. For instance, there are fifteen COG hospitals in Texas, most of them are in large metropolitan areas (Figure 5.1, in chapter 2).

However, the study found several literature gaps in childhood cancer disparities based on survival outcome. First, no reported study has investigated the underlying mechanistic pathways of race/ethnicity effect on overall survival for childhood cancer while mediated by socioeconomic status and spatial accessibility. Second, no study has examined how the total effect of race/ethnicity on childhood cancer survival operating through all mediating pathways decompose into natural direct and indirect effect.

The purpose of this current study was to integrate newly developed causal mediation analysis for childhood cancer survival analysis. The study investigated the effect of race/ethnicity on overall survival of childhood cancer patients while mediated through socioeconomic status and spatial accessibility mediators. The study compared 5-year overall survival for Hispanics and African-Americans childhood cancer using non-Hispanic whites as a reference. Also, the study examined the racial/ethnic differences in overall survival based on the International Classification of Childhood Cancer (ICCC-3) major site groups (Kaatsch, 2010). The current project selected the state of Texas as the study area because of its diverse population group, especially third-largest Hispanic population (Hamilton et al., 2016) which provide a distinct opportunity to study childhood cancer disparities.

The concept of 'mediation' was first introduced by Robert S. Woodworth in a psychological investigation to describe the pathway between stimulus and response in a Stimulus-Organism-Response model (Woodworth, 1948). Later on, this concept came into play a very important role in psychology, social science, behavior research and even in epidemiology. Simple analytic considerations of mediators in a model describing the causal chain (Baron & Kenny, 1986) inspired mediation analysis to put forward. Researchers now not only focus on the relationship between exposure and response but also the underlying mechanism of risk factors mediating the relationship (Ying Fan, 2014). In order to clearly understand the causal pathways from exposure to an outcome, Lange & Hansen (2011) employed a counterfactual framework that can measure natural direct and indirect effects for time-to-event data using an additive hazard model (Lange & Hansen, 2011). Mediation analysis has been implemented in multiple disciplines,

especially epidemiology and public health research (Kehm et al., 2018; Rochon, Du Bois, & Lange, 2014). The proportional hazard model is very common in epidemiologic research. In this model, the total effect is the product of natural direct and indirect effect (VanderWeele, 2012). The natural direct effect of exposure on outcome and the natural indirect effect operating through an intervening variable (mediator) tend to reflect specific causal pathways between exposure and outcome.

Childhood cancer disparity in Texas adopted a conceptual framework described in chapter one (Figure 1.1). Based on the framework, we selected socioeconomic status and spatial accessibility as determinants of health outcome. The details of the construction of socioeconomic status factors and spatial accessibility to specialized COG hospitals will be found in chapter two. Then we identified vulnerable population group using those determinants as a mediator in overall survival for childhood cancer patients. Finally, the study provided some recommendation for long-term policy making to eliminate SES and racial/ethnic disparities.

6.2 Data and Methodology

6.2.1 Study Population

The study employed statewide childhood cancer data limited to cases of individuals age between 0 to 19 years from the Texas Cancer Registry (TCR) in the Texas Department of State Health Services (TDSHS). There were 7700 reported childhood cancer cases in the state of Texas from 2005 to 2014. The last possible day of follow-up was December 31, 2014. The study protocol of this study and the use of the data was approved from the Institutional Review Boards (IRB) of Texas State University and the Texas Department of State Health Service.

6.2.2 Study Variables

6.2.2.1 Individual-level variables

This study included three major racial group: Non-Hispanic white, Hispanics and African-Americans in Texas. There was a small proportion (3.91%) of the reported cases for Native Americans, Asians, and other racial groups. Individual-level variables are race/ethnicity, age at diagnosis, stage at diagnosis and tumor grade, etc. Childhood cancer cases at diagnosis were categorized into localized, regional and distant stage based on the Surveillance Epidemiology End Result (SEER) program from the National Cancer Institute (NCI). The relative proportion of the *in situ* and localized, regional, distant, and not applicable or unstaged was 29% (2157), 11% (835), 43% (3177), and 17 % (1230) respectively. Based on the clinical and pathological information, *in situ* and the localized stage was categorized as early stage whereas regional and distant stage was characterized as late-stage. The study excluded cases with not applicable and unknown stage from the study for mediation analysis.

6.2.2.2 Contextual-level variables

The study used socioeconomic status (SES) factor which was constructed based on including percent unemployment, percent below poverty, median household income, percent household without a car. We also used contextual variable spatial accessibility to Children Oncology Group (COGs) hospitals for causal mediation analysis.

6.2.3 Methodology

The study used factorial analysis discussed in chapter two to analyze the covariation among the observed variables. This method helps to identify a number of latent factors such as socioeconomic status (SES) accounted for most of the variation

among the observed variables. Enhanced 2-step floating catchment area (E2SFCA) method (Luo & Qi, 2009) (details in chapter 2) was used to measure relative spatial access to Children Oncology Groups (COG) medical services. These continuous variables were summarized into high and low, incorporated in different stages of survival analysis.

The Cox proportional hazards regression or Cox regression method is the most popular regression method for survival analysis. The relationship between race/ethnicity and overall survival was measured using the Cox proportional hazards model with robust variance estimator. In this model, hazard ratio is the measure of effect (risk of failure) which is analogous to an odd ratio. Individual-level variables including diseases characteristics such as age, sex, and stage at diagnosis were assumed to control for confounding.

Mediation analysis was used based on the counterfactual framework (Pearl, 2011) to measure to what extent a point exposure is mediated by an intermediate variable (mediator) on the causal pathway between exposure and the outcome (Lange, Vansteelandt, & Bekaert, 2012; Tchetgen Tchetgen, 2013). The following acyclic diagram (Figure 6.1) shows the causal structure inferred throughout the analysis.

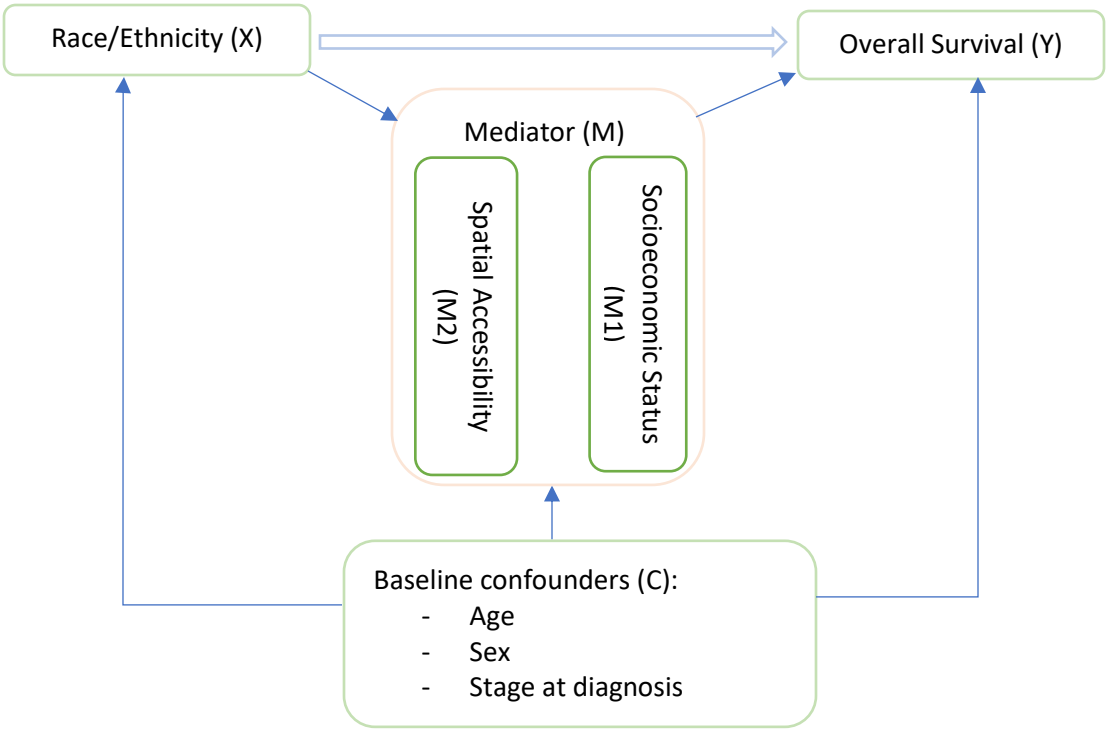

Figure 6.1 Mediation diagram with exposure race/ethnicity (X), mediator (M), outcome (Y), and covariates (C).

In the mediation diagram, X is the observed exposure of interest race/ethnicity, M a dichotomous potential mediator (High and Low), Y a dichotomous outcome and C denote a set of baseline confounders not affected by the exposure. When establishing the model parameter and the relationships between exposure-outcome, exposure-mediator, or mediator-outcome, it is assumed that there are no unmeasured confounders (Lange et al., 2012).

Based on the original counterfactual framework proposed by Pearl (2011), he later established that regardless of statistical model, the total effect can be decomposed into natural direct and indirect effects (Pearl, 2005; Robins & Greenland, 1992). In this model, we used all variables as a binary that was allowed to create counterfactual variables, possibly contrary to the fact for each subject (Lange et al., 2012). The causal

mediation analysis measured the extent to which the effect of race/ethnicity X on overall survival Y, mediated through mediator M (Socioeconomic Status (M1) and spatial accessibility (M2)) controlling for baseline confounders C, which is considered as indirect effects (IE). This model also measured the direct effect (DE) of race/ethnicity on overall survival assuming that exposure could be change without inducing a change in the mediator. The model reports total effects (TE) which is the aggregation of these two effects. The details of this method could be found elsewhere (Lange et al., 2012; VanderWeele, 2012; VanderWeele & Vansteelandt, 2010).

Confidence intervals for mediation effect were generated using a minimum of 500 bootstrap simulations. Simple random cluster sampling accounts for clustering of cases within census tracts. Independence of the two mediators was tested using logistic regression of spatial accessibility on socioeconomic status adjusting for other confounders. It is required to have mutually independent mediators for multiple pathways analysis when mediators exhibit conditional relationships on exposure and confounders (Lange et al., 2012; Rochon et al., 2014).

The study also performed sensitivity analysis using one binary mediator representing spatial accessibility and socioeconomic status considering that two mediators operate separately of each other. Survival curves were generated using the Kaplan-Meier Non-parametric method based on the survival function of standardized residuals (Kaplan & Meier, 1958). The study used the log-rank test to compare survival between two racial groups. The null hypothesis is that there is no difference between these two groups in terms of survival. All the analyses were performed in R version 3.5.0

(R Core Team, 2018) using ‘survival’ (Therneau & Lumley, 2018), ‘geepack’ (Højsgaard, Halekoh, & Yan, 2006) and ‘rms’ (Harrell, 2018) packages.

6.3 Results

First, we characterized childhood cancer dataset based on the International Classification of Childhood Cancer (ICCC). There 12 major site group recognized for childhood cancer (ICCC, 2011). The following Table 6.1 shows the major characteristics of cancer site in children. Descriptive statistics by cancer site group provided information on individual-level racial/ethnic, diseases characteristics and contextual-level feature such as socioeconomic status. Leukemias, myeloproliferative diseases, and myelodysplastic diseases had the highest number of cases, the average age at diagnosis was less than six years (SD 4.3 years), survival means 23.51 months. It is noted that most of the cases were diagnosed in the late stage (99.69%) and around half of them lived in the socioeconomically underprivileged area. Central Nervous System (CNS) and miscellaneous intracranial and intraspinal neoplasms had the second highest number of cases with an average age at diagnosis and survival of 7.24 (SD 4.6) years and 34.46 months respectively. A significant proportion of childhood cancer patients were lived in the affluent neighbourhood. However, a substantial number of them (61.61 %) were diagnosed in the late-stage.

Table 6.1 Characteristics of Childhood Cancer cases diagnosed from 2005 to 2014

Site Group	No.	Race/Ethnicity						Stage at Diagnosis (%)			Tract-level SES, %			
		NHW	HIS	AA	Age at Diagnosis mean (SD)	Female	Survival mean (SD), mo	Early-Stage	Late-Stage	Unknown Stage	Q1	Q2	Q3	Q4
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	2260	861	1222	177	5.98 (4.3)	1045	23.51 (34.0)	0.22	99.69	0.09	**28.3**	22.5	22.6	26.6
II. Lymphomas and reticuloendothelial neoplasms	797	333	383	81	8.97 (4.9)	295	31.84 (32.3)	27.23	61.61	11.17	**27.2**	22.6	25.7	24.5
III. CNS and miscellaneous intracranial and intraspinal neoplasms	1944	923	813	208	7.24 (4.6)	944	34.46 (34.5)	54.99	11.01	34.00	**30.3**	26.5	20.5	22.6
IV. Neuroblastoma and other peripheral nervous cell tumors	295	160	95	40	3.45 (3.1)	139	31.38 (31.5)	20.68	68.47	10.85	**33.2**	29.2	19.3	18.3
V. Retinoblastoma	115	36	52	27	2.10 (1.9)	65	31.39 (35.3)	57.39	35.65	6.96	26.1	20	23.5	30.4
VI. Renal tumors	332	134	142	56	3.80 (2.9)	181	28.98 (33.1)	34.64	59.64	5.72	**34.6**	18.7	22.6	24.1
VII. Hepatic tumors	91	36	47	8	3.85 (3.9)	37	26.71 (29.7)	38.46	54.95	6.59	**36.3**	24.2	12.1	27.5
VIII. Malignant bone tumors	273	114	126	33	10.5 (4.1)	123	34.17 (30.2)	43.22	45.05	11.72	**30.0**	24.5	20.9	24.5
IX. Soft tissue and other extraosseous sarcomas	601	280	244	77	7.80 (4.9)	260	33.58 (33.6)	29.62	27.95	42.43	**28.5**	25.6	22.6	23.3
X. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	250	94	130	26	10.76 (5.3)	134	35.09 (31.6)	51.6	36.4	12	**32**	18.8	22	27.2
XI. Other malignant epithelial neoplasms and malignant melanomas	425	210	177	38	12.08 (4.2)	275	32.97 (31.3)	38.59	42.35	19.06	**30.1**	26.1	23.1	20.7
XII. Other and unspecified malignant neoplasms	34	10	20	4	7.35 (5.5)	16	29.94 (34.7)	20.59	29.41	50	17.6	14.7	32.4	35.3

Abbreviation: NHW, Non-Hispanic White; HIS, Hispanics, AA, African Americans

Hispanics contributed the highest number of cases in Leukemias, myeloproliferative diseases, and myelodysplastic, and Lymphomas and reticuloendothelial neoplasms diseases. There were only 34 cases for others, and unspecified malignant neoplasms and 20 of them were Hispanics. The average age and survival were 7.35 years and around 30 months respectively, and 35 % of them were lived in very low socioeconomic status. The number of female cases was comparatively lower than male across cancer site group.

The next main question was to see how race/ethnicity effect on survival while mediated by socioeconomic status and spatial accessibility mediators. Before we ran the mediation analysis, we checked whether these two mediators were mutually exclusive using logistic regression analysis. Independence of two mediators test for African-American and Non-Hispanics whites was nonsignificant ($P = 0.2456$) indicating that two mediators were mutually independent. However, independence to two mediators test turned out to be significant ($P < 0.001$) for Hispanic and Non-Hispanic whites suggesting mediators were not consistent with the assumption of independence. Table 6.2 shows the mediation effect of race/ethnicity on overall survival while mediated by spatial accessibility and socioeconomic status.

Table 6.2 Survival disparities of African-Americans and non-Hispanic whites from 2005 to 2014

Variables	Total Effect of Race on survival through all mediating pathways		Direct Effect of race on survival after Blocking SES & SA pathways		Indirect Effect of race on survival operating through SES & SA pathways		Media -ted by SES & SA, %
Race/Eth-nicity	**Mortality HR**	**95 % CI**	**Mortality HR**	**95 % CI**	**Mortality HR**	**95 % CI**	
NHW	Reference (1.00)						
AA	3.626	1.87 - 6.62	1.536	1.23 - 1.88	2.360	1.52 - 3.53	66.7
HIS	1.228	0.80 - 1.93	1.071	0.93 - 1.25	1.146	0.86 - 1.55	66.7
Sensibility analysis							
NHW	Reference (1.00)						
AA	2.301	2.30 - 2.30	1.517	1.52 - 1.52	1.517	1.52 - 1.52	0.50
HIS	1.121	1.12 - 1.12	1.059	1.06 - 1.06	1.059	1.06 - 1.06	0.50

Abbreviation: NHW, Non-Hispanic whites; AA, African-Americans, HIS, Hispanics; HR, Hazard ratio; CI, Confidence Interval
Adjusted for Age, Sex, and stage at diagnosis; Bootstrapping was used for standard error

Considering all cancer site group, African-American had statistically significant higher hazard of death compared with non-Hispanic whites. Two mediators significantly contributed to racial/ethnic survival disparities. The hazard ratio was as high as 3.626 (95% CI: 1.87 to 6.62), and the confidence interval did not include 1, meaning not statistically significant. The total effect was decomposed into direct HR of race/ethnicity of 1.536 (95% CI: 1.23 to 1.88) and an indirect HR for spatial accessibility and SES mediators of 2.360 (95% CI: 1.52 to 3.53). On the other hand, Hispanics also had a significantly higher hazard of death compared with their white counterpart (HR 1.228, 95% CI: 0.80 – 1.93). The total mortality hazard for Hispanic and whites also decomposed into direct HR of 1.071 (95% CI: 0.93 to 1.25) and an indirect HR for both mediators of 1.146 (95% CI: 0.86 to 1.55). In both cases, about 67 % of the effect of race/ethnicity is mediated by spatial accessibility and socioeconomic status.

Sensibility analysis was performed using a single binary mediator reflecting optimal adherence to both mediators in a sense that both spatial accessibility and socioeconomic status are considered optimal. Logistic regression result shows that

race/ethnicity has a significant effect on the aggregated mediator, with an odd ratio of 2.37 and 4.94 in favor of African-Americans and Hispanics respectively.

Table 6.3 shows the childhood cancer survival disparities in Non-Hispanic whites and African-Americans. African-Americans showed a significantly higher hazard ratio for most of the cancer types, especially for leukemia. These might be overestimation for a small number of African-American cases compared to whites. SES and spatial accessibility significantly contributed to African-Americans and white survival disparities for cancer site group including lymphomas, CNS tumors, soft tissue sarcomas, and germ cell tumors. Other cancer site groups did not provide any meaningful result due to an unusually small number of cases.

Table 6.3 Survival disparities of African-Americans and non-Hispanic whites based on site group

Variables NHW/AA	Total Effect of Race on survival through all mediating pathways		Direct Effect of race on survival after Blocking SES & SA pathway		Indirect Effect of race on survival operating through SES & SA pathway		Media -ted by SES & SA, %
Site Group	Mortality HR	95 % CI	Mortality HR	95 % CI	Mortality HR	95 % CI	
I.	10.182	7.12 - 20.15	2.167	1.92 - 2.72	4.698	3.69 - 7.40	66.7
II.	2.394	0.06 - 31.94	1.338	0.39 - 3.17	1.790	0.15 - 10.06	“
III.	2.406	0.82 - 6.65	1.340	0.94 - 1.88	1.796	0.88 - 3.54	“
IV.*							
V.*							
VI.*							
VII.	0.128	0.01 - 1.59	0.504	0.23 - 1.13	0.254	0.05 - 1.33	“
VIII.	3.888	0.22 - 88.98	1.572	0.60 - 4.47	2.473	0.36 - 19.93	“
IX.	4.841	0.73 - 40.62	1.692	0.90 - 3.44	2.862	0.81 - 11.81	“
X.*							
XI.	0.592	0.03 - 13.64	0.840	0.29 - 2.38	0.705	0.09 - 5.70	“
XII.*							

Abbreviation: NHW, Non-Hispanic whites; AA, African-Americans; HR, Hazard ratio; CI, Confidence Interval

*Results not reported due to low observed frequency for at least one racial group

Adjusted for Age, Sex, and stage at diagnosis; Bootstrapping was used for standard error; Roman number refer to table 6.1

Figure 6.2 shows the Kaplan-Meier Non-parametric survival curve based on the survival function of standardized residuals. There were 422 cases out of 3191 non-Hispanic white who faced death event during the follow-up period of 11 years quarter months. On the other hand, during the same follow-up period, 156 death events were observed out of 772 African-Americans cases. The proportion of cases surviving past five years (60 months) were 78 % and 70 % for non-Hispanic white and African-American respectively. There were 605 and 146 cases at risk after 5-years of survival for Non-Hispanic whites and African-Americans. The median survival is approximately 130 months for both non-Hispanic whites and African-Americans. The global log-rank test resulted in high chi-square value (χ^2:19.1; 1df; $P < 0.001$), suggesting to these two survival curves are not identical.

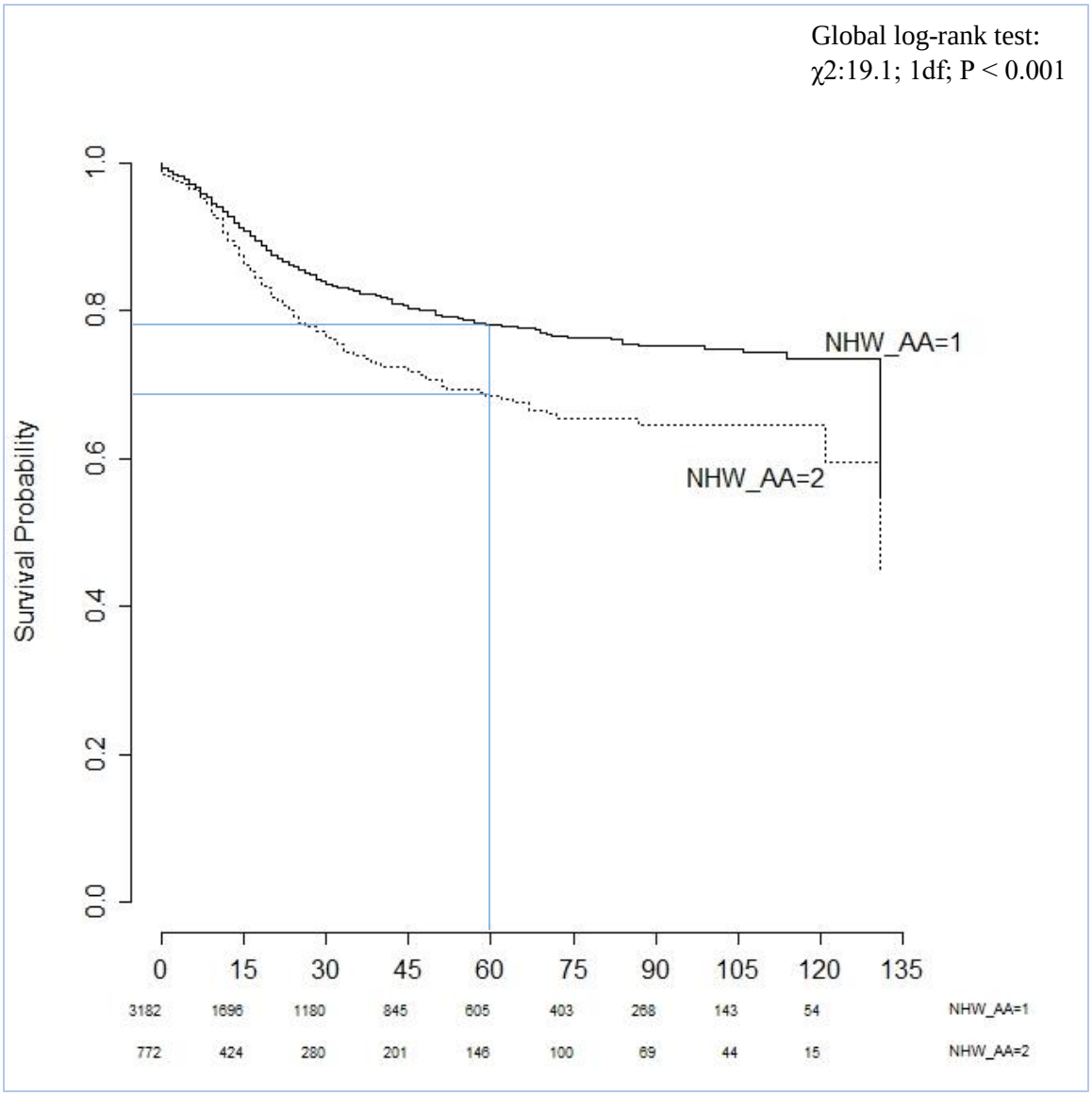

Figure 6.2 Kaplan-Meier survival curves for Non-Hispanic whites and African-Americans

Table 6.4 shows the childhood cancer survival disparities in Non-Hispanic whites and Hispanics. The study found that SES and spatial accessibility significantly mediated to Hispanics and Non-Hispanic whites survival disparities for several cancer site groups. Hispanics children had an increased risk of 118 % of mortality hazard for leukemias compared with Non-Hispanic whites. Hispanics also showed significantly higher hazard

ratio for other cancer types such as CNS tumors, Malignant bone tumor, Soft tissue and other extraosseous sarcomas, and Other malignant epithelial neoplasms and malignant melanomas.

Variables (NHW/HIS)	Total Effect of Race on survival through all mediating pathways		Direct Effect of race on survival after Blocking SES & SA pathway		Indirect Effect of race on survival operating through SES & SA pathway		Mediat-ed by SES & SA, %
Site Group	Mortality HR	95 % CI	Mortality HR	95 % CI	Mortality HR	95 % CI	
I.	2.180	0.92 - 4.99	1.300	0.97 - 1.71	1.680	0.94 - 2.92	66.7
II.	0.720	0.09 - 4.77	0.896	0.45 - 1.68	0.803	0.20 - 2.84	"
III.	1.831	0.91 - 3.93	1.223	0.97 - 1.58	1.497	0.94 - 2.49	"
IV.*							
V.*							
VI.*							
VII.	0.198	0.05 - 3.57	0.582	0.37 -1.51	0.339	0.14 - 2.31	"
VIII.	1.148	0.20 - 9.48	1.047	0.59 - 2.12	1.097	0.34 - 4.48	"
IX.	1.917	0.30 - 8.85	1.242	0.67 - 2.07	1.543	0.44 - 4.28	"
X.*							
XI.	1.675	0.07 47.06	1.188	0.41 - 3.61	1.410	0.17 - 13.03	"
XII.*							

Table 6.4 Survival disparities of Hispanics and non-Hispanic whites based on site group
Abbreviation: NHW, Non-Hispanic whites; His, Hispanics; HR, Hazard ratio; CI, Confidence Interval
*Results not reported due to low observed frequency for at least one racial group
Adjusted for Age, Sex, and stage at diagnosis; Bootstrapping was used for standard error; Roman number refer to table 1

Figure 6.3 shows the Kaplan-Meier survival curves for Non-Hispanic whites and Hispanics**.** During the same follow-up period of 11 years quarter months, 528 death events were observed out of 3451 Hispanics children. The proportion of cases surviving past five years (60 months) were 78 % and 76 % for non-Hispanic white and Hispanics respectively. There were 643 and 494 cases at risk after 5-years of survival for Non-Hispanic whites and Hispanics. The global log-rank test provided very small chi-square value (χ^2: 1.30; 1df; P = 0.30). We have significant evidence to show that these two survival curves are not different. It is apparent that two curves also crossed each other in course of time.

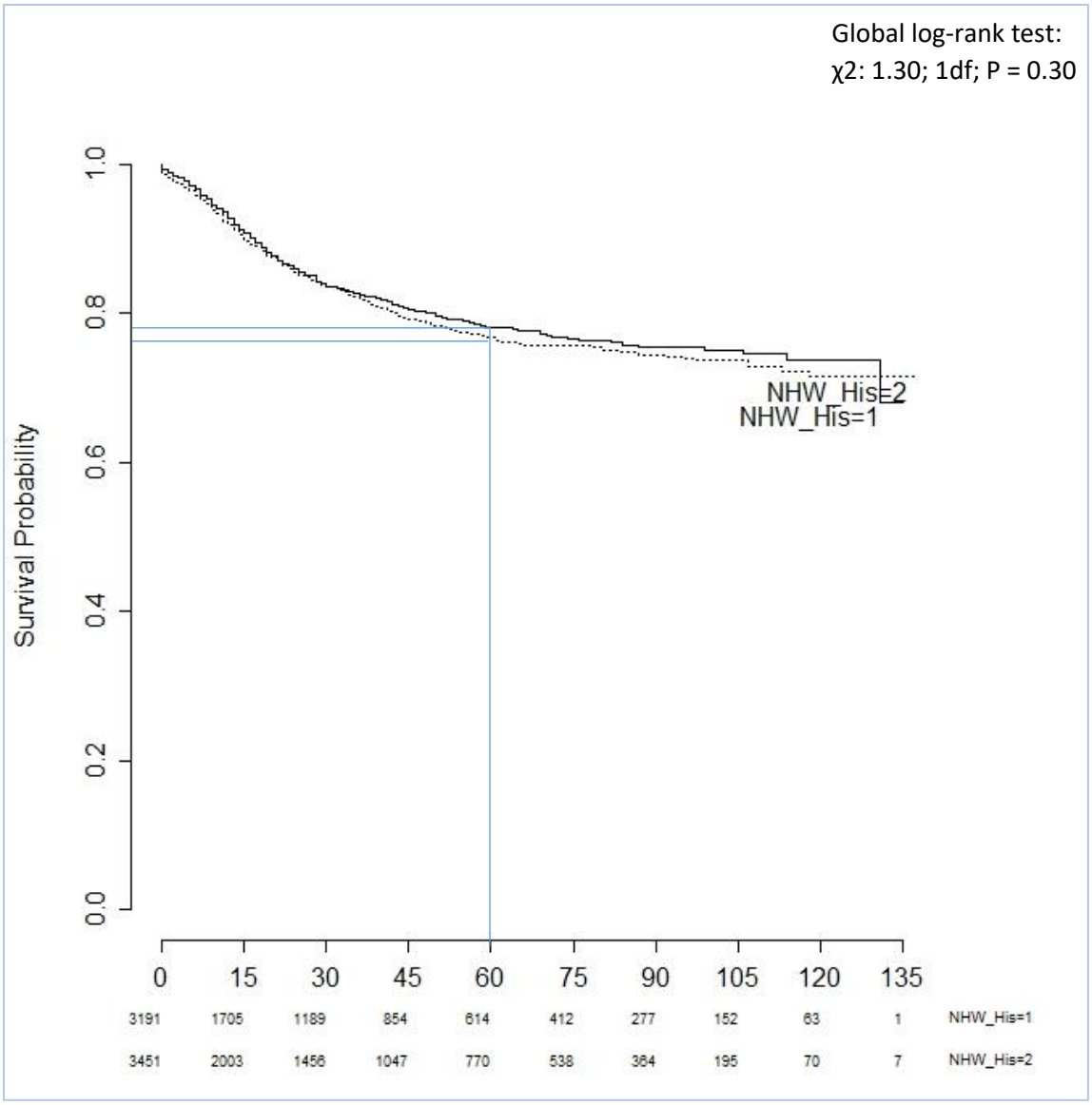

Figure 6.3 Kaplan-Meier survival curves for Non-Hispanic whites and Hispanics

6. 4 Discussion

Childhood cancer characterization based on twelve major site group provided a thoughtful insight for cancer patients under the age of nineteen in the state of Texas. Unlike other research that encompasses large dataset form SEER 18 registries (Kehm et al., 2018), we were not able to classify based on specific cancer types. We excluded those cases that were unstaged or not applicable defined by the Texas Cancer Registry.

The average age at diagnosis ranges from 2.10 years (SD 1.9) for retinoblastoma to 12.08 (SD 4.2) for other malignant epithelial neoplasms and malignant melanomas. There were few cases over the age of 14 to 19 years old. The number of male cases was high for most of the cancer site groups except for CNS, renal tumor, and germ cell tumor and, other malignant epithelial neoplasms and malignant melanomas. The survival means for almost all cancer site group ranges from 2-3 years. Considering stage at diagnosis for all cases, the percentage of late-stage diagnosis was significantly high which indicate a lower survival rate. The study also reported socioeconomic status summary information for childhood cancer site groups. Though from visual observation it seems most of the cancer site groups fall into the high socioeconomic status neighborhood. Speculating socioeconomic status from a sharp quantile cut-off is hard. Therefore, we used high and low category of socioeconomic status for mediation analysis. We followed the same techniques for spatial accessibility as well.

The total effect of race/ethnicity on survival was estimated using the standard Cox proportional hazard model adjusting for all known baseline confounders. The result indicated that race/ethnicity (African-Americans versus Non-Hispanic whites) had a statistically significant effect on overall survival controlling for confounders. We also investigated the effect of race/ethnicity on the two binary mediators optimal socioeconomic status and optimal spatial accessibility. The study found statistically significant ($P < 0.001$) results for socioeconomic status which indicate that better socioeconomic status in the African-American neighborhood in census tract level associated with higher survival. The odd ratio for optimal spatial accessibility was 1.22 in favor of African-Americans, which was not statistically significant. The study did not

find statistically significant effect of race/ethnicity when it comes to non-Hispanic whites and Hispanics on overall survival mediated by socioeconomic status and spatial accessibility. The sensibility analysis results included effect estimates, and confidence intervals roughly corroborate with the primary analyses.

The Kaplan-Meier survival test indicated that the survival probabilities for Non-Hispanic whites are higher than the survival probabilities for African-Americans, suggesting a survival benefit. There is a statistically significant difference in survival between these two groups based on the non-parametric log-rank test. The survival benefit remained stable even after controlling for known baseline confounders, also adjusting for cases within census tracts in a multivariable Cox proportional hazard model. However, both survival and global log-rank test for Hispanics and Non-Hispanic whites indicated that there was no significant difference in survival between these two groups. Our results corroborate with previous population-based SEER 9 registries studies from 1995 -1999 (Linabery & Ross, 2008), Acute Lymphoblastic Leukemia (ALL) cases from 1973 – 1999 (Kadan-Lottick et al., 2003), and ALL cases from 1983-1995 in Children's Cancer Group (CCG) (Bhatia et al., 2002).

Cancer outcome is known to be impacted by the difference in socioeconomic status. This important indicator has not been examined enough for childhood cancer survival analysis. SES was not found significantly associated with delay diagnosis (Dang-Tan et al., 2010; Haimi, 2004; Martin et al., 2007) and although showing no indication of increasing the risk of childhood cancer (Marquant et al., 2016). In this study, SES was constructed based on multiple indicators such as percent below poverty, percent unemployed, median household income, and percent household without a car. Also, the

second chapter of this dissertation reported that most of the rural area in Texas is highly inaccessible to COG services which alleviate the quality and span of life of children with cancer (Figure 5.1).

There are several strengths of this current research. First, the study is based on population-based state-wide cancer registry dataset of childhood cancer which reduces the potential for selection bias relative to hospital-based studies. Second, the study was able to incorporate socioeconomic status and spatial accessibility as important mediators for a small area unit, census tracts. Third, the study revealed that race/ethnicity had a significant effect on overall survival while mediated by socioeconomic status and spatial accessibility. African-American children with cancer showed statistically significant different survival results compared with their white counterpart.

This study has a couple of limitations to be noted when interpreting the results. First, there were few cases for African-Americans which may overestimate the results when compared with non-Hispanic white. Second, the Kaplan-Meier survival curve for Hispanics and Non-Hispanic whites had crossed each other. The hazard ratio for this model would not be a useful measure because the assumption for the model might not hold true as those curves aligned some areas (Sedgwick, 2014). Third, the Independence of two mediators test for non-Hispanic white and Hispanics appears to be significant. Someone has to be extra cautious while performing mediation analysis for these racial group using the same mediators. Mutually independent mediators are required for analysis of multiple pathways (Rochon et al., 2014).

6.5 Concluding Remarks and Policy Implication

Causal mediation analysis has got substantial attention in diverse research arena because of its potential to go beyond answering the complex mechanism of mediators accounting existing effect of exposure on outcome. Mediation analysis found a statistically significant effect of race/ethnicity (African-Americans versus non-Hispanics white) on the mediators onto overall survival. The survival analysis indicates that African-American had a much lower survival rate than their Non-Hispanic white counterpart. The study did not find statistically significant effect of race/ethnicity when it comes to non-Hispanic whites and Hispanics on overall survival mediated by socio-economic status and spatial accessibility. Also, the study did not find a significant difference in the survival of Hispanics and Non-Hispanic whites. The study also demonstrated that socioeconomic status and spatial accessibility significantly contribute to racial/ethnic survival disparities for specific cancer site group including Leukemia, CNS tumors, malignant bone tumors, and soft tissue sarcomas.

It is well reported that the effect of race/ethnicity on survival is closely associated with socioeconomic status. In particular, the socio-economic status of parents is an important determinant for childrens' health. Children are dependent on their parents and family for their well-being. Childhood cancer survivors living in a lower income household are more likely to be uninsured or face difficulties to obtain the required coverage. Moreover, one-fifth of the US population still live in rural areas. Accessibility to specialized health care facilities poses a greater challenge for families living in remote areas.

Substantial progress has been made toward overall survival in childhood cancer. Racial discrepancies in overall survival can be eliminated to some degree by equal enrollment on cooperative group trials. Children treated in clinical trial programs developed by COG appears to have a better outcome than non-specialized hospitals. Genetic differences in diseases biology may not be the only cause of racial/ethnic discrepancies in outcome; socioeconomic status is closely tied with the racial/ethnic origin and their access to and quality healthcare which eventually may affect the cancer outcome (Bhatia, 2011). Results from this study will contribute to developing effective childhood cancer intervention programs. Intervention program should be designed targeting children and adolescents with childhood cancer, in particular, African-Americans living in the remote and socioeconomically disadvantaged areas. Future study will examine racial and ethnic survival disparities for specific cancer types accounting for other potential mediators alongside socioeconomic status and spatial accessibility.

7. CONCLUSION

The last chapter consists of three sections. The first section of conclusion summarizes the results described in the three previous chapters. The second section outlines the contributions of this current research about childhood cancer disparities in Texas. The third section points out the limitations of this dissertation research and suggest the future direction of research of this important topic.

7.1 Summary of Results

The main purpose of this project was to investigate childhood cancer disparities in Texas. More specifically this study has three primary objectives: a) to investigate childhood cancer disparities in Texas from the perspective of three major social characteristics: geographic location, race/ethnicity, and socioeconomic status (SES); b) to examine the role of both individual-level variables and contextual-level variables in these disparities; c) to analyze the effect of race/ethnicity on overall survival of childhood cancer patients mediated through socioeconomic status and spatial accessibility mediators.

The first objective was attained by investigating childhood cancer disparities in the state of Texas using two test statistics measures (Risk difference and Risk Ratio) from the perspective of geographic location and race/ethnicity. There were total of 47 census tracts showed significantly higher late-stage diagnosis rate in Hispanics and most of them were located outside of metropolitan areas except for the Dallas-Fort Worth area. Likewise, the study also calculated childhood cancer disparities for African-Americans. There were 58 census tracts (out of 5265) that experienced significantly higher late-stage diagnosis rate when compared with non-Hispanic whites. However, most of the

significant census-tracts were located inside large metropolitan area such as the Dallas-Fort Worth and Houston areas.

The study also calculated the yearly late-stage diagnosis rate for significant census tracts for Hispanics and African-Americans. The temporal change in the yearly rate for African-Americans is high throughout the timeframe. However, Hispanics showed relatively better results for significant census tracts count and yearly rates of late-stage childhood cancer diagnosis.

The second objective was achieved in serval steps. First, we calculated the spatial access to COGs hospitals using the enhanced 2-step floating catchment area (E2SFCA) method. The relative spatial accessibility result showed that urban areas with high population density have easy access to COGs services compared to rural inhabitants. It is worth mentioning that most of the COGs hospitals are located in large metropolitan areas. Multilevel logistic regression was used to analyze how individual and contextual level factors impact the occurrence of childhood cancer late-stage diagnosis by race/ethnicity and other social varables. Individual level variables include race/ethnicity, age at diagnosis, stage at diagnosis and tumor grade. Contextual-level variables are SES, socio-cultural, socio-environmental (Percent Hispanics and percent African Americans), spatial access to COGs hospitals, percentage of health insurance coverage at the census tract level. The study revealed statistically significant difference in racial/ethnic and social determinants such as SES, socio-cultural factor, education, and percent health insurance coverage contributing to disparities of childhood cancer late-stage diagnosis. Hispanics had an elevated risk of late-stage diagnosis compared with non-Hispanic white even after adjusting for individual factor such as age and contextual-level factors including SES,

socio-cultural factors, education-level factor, percentage of African Americans, percentage of health insurance coverage, and spatial access to COG hospitals.

The study found a strong correlation between SES and childhood cancer stage at diagnosis. The relative proportion of childhood cancer cases diagnosed at a late-stage are high in socioeconomically disadvantaged neighborhoods. It was apparent that parental education was found an important factor for stage at diagnosis. Sociocultural factor which was constructed based on limited English-speaking household, average family size and percent Hispanics also found to be an important predictor for childhood cancer late-stage diagnosis. Finally, health insurance coverage can pose a major obstacle to adequate treatment and preventive healthcare services.

In achieving the third objective, the study used causal mediation analysis to examine the underlying mechanistic pathways of race/ethnicity effect on overall survival while mediated by two mediators such as socioeconomic status and spatial accessibility. The study revealed that African-American had statistically significant higher mortality hazard considering all cancer site group together compared with their non-Hispanic white counterpart. Although two mediators were not mutually exclusive for Hispanic and non-Hispanic white, Hispanic showed significantly higher mortality hazard. The indirect effect of race on survival operating through SES and spatial accessibility was higher for both Hispanics and African Americans. The sensibility analysis reported effect estimates which also corroborate with the primary result. In addition, the Kaplan-Meier survival test indicated that the survival probabilities for Non-Hispanic whites are higher than African-Americans, suggesting a survival benefit. The study found a statistically

significant difference in survival between these two racial groups. However, there was no significant difference in survival between Hispanics and Non-Hispanic whites.

7.2 Contribution

There are several contributions from this dissertation research. First, the key aspect of this dissertation research was to contribute our understanding of childhood cancer disparities form the perspective of geographic location, race/ethnicity, and other social domains. The study also explored the root cause of disparity integrating both individual and contextual level factors. Identifying risk factors contributing to cancer disparities is a challenging task as social structure is a complex phenomenon, and changes over time and space. This study identified a number of risk factors pertinent to childhood cancer late-stage diagnosis. Children are incapable of making the appropriate decision for their well-being. The study contributes to better understanding of multilevel social determinants of health attributed to most health inequalities.

Second, no reported study has examined spatial accessibility to specialized COGs hospitals and the role of spatial access in childhood cancer stage at diagnosis. This study provided a detailed picture of health care accessibility at the neighborhood level by taking into accounts GIS-based methodology that may better represent spatial variation in health care systems and accessibility. The study found that most of the rural areas in Texas is highly inaccessible to COG services which affect the quality and span of life of children with cancer.

Third, survival analysis was performed using a newly developed causal mediation analysis method. To the best of our knowledge, no reported study has explored the underlying mechanistic pathways of the effect of race/ethnicity on overall survival for

childhood cancer mediated by socioeconomic status and spatial accessibility. This study enhanced our knowledge and understanding of these underlying factors (mediators) by observing multiple level effect on childhood cancer outcomes.

Fourth, the study will have policy implications. Better understating of the factors associated with the childhood cancer disparities will help develop more effective intervention programs in targeted regions. The study investigated relationships between the geographic pattern of diseases distribution, physical and social environmental condition, with the help of GIScience that is capable of bringing rich information database closely associated with spatial analysis method. Additionally, the results will contribute to the geographical resource allocation system which in turn help to facilitate preventive health care service and alleviate the diseases burden in children.

7.3 Limitations and Future work

This dissertation research suffers from several limitations. First, The results of this study are restricted to the variability of geographic location and race/ethnicity in relation to stage at diagnosis of childhood cancer. We considered all cases are located in the same location inside each census tracts. This is somewhat acceptable for a regular small census tract size. People tend to live in the same neighborhood based on their race/ethnicity and SES. Second, the study excluded 46 census tracts record (0.87 of the total) while processing sociodemographic dataset due to inadequate information. Also, we excluded 1232 (16.61% of the total) cases from the logistic regression analysis because of unknown/not applicable stage at diagnosis. Moreover, the study excluded tumor grade from the analysis because grade descriptions were unknown (not stated, or not applicable) for more than 50% cases.

Third, accessibility analysis was performed assuming that population lives in the centroid of each census tracts, that is acceptable for census tracts that are small in size. However, in the real world the distribution of shape and size of census tracts, and the number of population varies in time and space. The study used 300-minutes maximum travel time as focal catchment area (FCA) dimension for network travel impedance/cost. This FCA dimension may not work with limited resource availability such as transportation services. The study also considered each COG center provide equal services regarding medical professionals and logistics which is not realistic and calls for further investigation. Future accessibility analysis should include different FCA dimensions in conjunction with different modes of transportation.

Fourth, there were few African-American cases which may introduce bias in the results when compared with non-Hispanic white. The independence test for two mediators (SES and spatial accessibility) appears to be significant for Hispanic and non-Hispanic white. Extra care should be given when interpreting the casual mediation analysis results for Hispanics and non-Hispanic white. It is suggested that future studies should account for other mediators such as socio-cultural factors, education-level, and health insurance coverage.

REFERENCE CITED

Abdelkhalek, E R, L M Sherief, N M Kamal, and R M Soliman. 2014. “Factors Associated with Delayed Cancer Diagnosis in Egyptian Children.” *Clinical Medicine Insights* 8: 39–44. https://doi.org/10.4137/CMPed.S16413.RECEIVED.

Abrahao, Renata, Daphne Y. Lichtensztajn, Raul C. Ribeiro, Neyssa M. Marina, Ruth H. Keogh, Rafael Marcos-Gragera, Sally L. Glaser, and Theresa H M Keegan. 2015. “Racial/Ethnic and Socioeconomic Disparities in Survival among Children with Acute Lymphoblastic Leukemia in California, 1988-2011: A Population-Based Observational Study.” *Pediatric Blood and Cancer* 62 (10): 1819–25. https://doi.org/10.1002/pbc.25544.

Abraho, Renata, Ruth H. Keogh, Daphne Y. Lichtensztajn, Rafael Marcos-Gragera, Bruno C. Medeiros, Michel P. Coleman, Raul C. Ribeiro, and Theresa H M Keegan. 2016. “Predictors of Early Death and Survival among Children, Adolescents and Young Adults with Acute Myeloid Leukaemia in California, 1988-2011: A Population-Based Study.” *British Journal of Haematology* 173 (2): 292–302. https://doi.org/10.1111/bjh.13944.

Adam, Martin, Corina S Rueegg, Kurt Schmidlin, Adrian Spoerri, Felix Niggli, Michael Grotzer, Nicolas X Von Der Weid, et al. 2016. “Socioeconomic Disparities in Childhood Cancer Survival in Switzerland.” *International Journal of Cancer* 2866: 2856–66. https://doi.org/10.1002/ijc.30029.

Aday, Lu Ann, and Ronald Andersen. 1974. “A Framework for the Study of Access to Medical Care.” *Health Services Research* 9 (3): 208–20. https://doi.org/10.3205/psm000089.

Ahrens, Wolfgang, and Iris Pigeot. 2014. *Handbook of Epidemiology: Second Edition*. *Handbook of Epidemiology: Second Edition*. https://doi.org/10.1007/978-0-387-09834-0.

Ahrensberg, J M, F Olesen, R P Hansen, H Schrøder, and P Vedsted. 2013. “Childhood Cancer and Factors Related to Prolonged Diagnostic Intervals: A Danish Population-Based Study.” *British Journal of Cancer* 108 (6): 1280–87. https://doi.org/10.1038/bjc.2013.88.

American Cancer Society. 2015. “Cancer Facts & Figures 2015.” *Cancer Facts & Figures 2015*, 1–9. https://doi.org/10.1097/01.NNR.0000289503.22414.79.

Araz, Nilgun Col, and Elif Guler. 2015. “Delays in Diagnosis of Childhood Cancer in Southeastern Turkey and the Associated Factors.” *Pediatric Hematology and Oncology* 32 (2): 153–63. https://doi.org/10.3109/08880018.2013.874511.

Armenian, Saro H., Wendy Landier, Melissa M. Hudson, Leslie L. Robison, and Smita Bhatia. 2013. “Children’s Oncology Group’s 2013 Blueprint for Research: Survivorship and Outcomes.” *Pediatric Blood Cancer* 60 (6): 1063–68. https://doi.org/10.1002/pbc.24422.

Austin, Mary T., Hoang Nguyen, Jan M. Eberth, Yuchia Chang, Andras Heczey, Dennis P. Hughes, Kevin P. Lally, and Linda S. Elting. 2015. “Health Disparities Are Important Determinants of Outcome for Children with Solid Tumor Malignancies.” *Journal of Pediatric Surgery* 50 (1): 161–66. https://doi.org/10.1016/j.jpedsurg.2014.10.037.

Austin, S. Bryn, Steven J. Melly, Brisa N. Sanchez, Aarti Patel, Stephen Buka, and Steven L. Gortmaker. 2005. “Clustering of Fast-Food Restaurants around Schools: A Novel Application of Spatial Statistics to the Study of Food Environments.” *American Journal of Public Health* 95 (9): 1575–81. https://doi.org/10.2105/AJPH.2004.056341.

Bailey, Helen D., Bruce K. Armstrong, Nicholas H. De Klerk, Lin Fritschi, John Attia, Rodney J. Scott, Elizabeth Smibert, and Elizabeth Milne. 2011. “Exposure to Professional Pest Control Treatments and the Risk of Childhood Acute Lymphoblastic Leukemia.” *International Journal of Cancer* 129 (7): 1678–88. https://doi.org/10.1002/ijc.25769.

Bailey, Trevor, and Anthony. Gatrell. 1995. *Interactive Spatial Data Analysis*. *Interactive Spatial Data Analysis*. https://doi.org/10.1016/0277-9536(95)00183-2.

Bernstein, Kyle T., Frank C. Curriero, Jacky M. Jennings, Glen Olthoff, Emily J. Erbelding, and Jonathan Zenilman. 2004. “Defining Core Gonorrhea Transmission Utilizing Spatial Data.” *American Journal of Epidemiology* 160 (1): 51–58. https://doi.org/10.1093/aje/kwh178.

Besag, Julian, and James Newell. 1991. “The Detection of Clusters in Rare Diseases.” *Journal of the Royal Statistical Society.* 154 (1): 143. https://doi.org/10.2307/2982708.

Bhatia, Smita, Harland N. Sather, Nyla A. Heerema, Michael E. Trigg, Paul S. Gaynon, and Leslie L. Robison. 2002. “Racial and Ethnic Differences in Survival of Children with Acute Lymphoblastic Leukemia.” *Blood* 100 (6): 1957–64. https://doi.org/10.1182/blood-2002-02-0395.

Bona, Kira, Traci M. Blonquist, Donna S. Neuberg, Lewis B. Silverman, and Joanne Wolfe. 2016. “Impact of Socioeconomic Status on Timing of Relapse and Overall Survival for Children Treated on Dana-Farber Cancer Institute ALL Consortium Protocols (2000–2010).” *Pediatr Blood Cancer* 2016 (63): 1012–1018. https://doi.org/10.1002/pbc.25928.

Borugian, Marilyn J, John J Spinelli, Zenaida Abanto, Chen Lydia Xu, Russell Wilkins, Marilyn J Borugian, John J Spinelli, Zenaida Abanto, Chen Lydia Xu, and Russell Wilkins. 2011. “Neighbourhood Income Neighbourhood Income,” no. 82.

Bosetti, Cristina, Paola Bertuccio, Liliane Chatenoud, Eva Negri, Fabio Levi, and Carlo La Vecchia. 2010. “Childhood Cancer Mortality in Europe, 1970-2007.” *European Journal of Cancer* 46 (2): 384–94. https://doi.org/10.1016/j.ejca.2009.09.011.

Brown, B J, B O James, S O Ajayi, O A Ogun, and R E Oladokun. 2009. “Factors Influencing Time to Diagnosis of Childhood Cancer in Ibadan, Nigeria.” *African Health Sciences* 9 (4): 247–53. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3074401&tool=pmcentrez&rendertype=abstract.

Byers, Tim. 2010. “Two Decades of Declining Cancer Mortality: Progress with Disparity.” *Annual Review of Public Health* 31: 121–32. https://doi.org/10.1146/annurev.publhealth.121208.131047.

Cai, Qiang, Gerard Rushton, and Budhendra Bhaduri. 2012. “Validation Tests of an Improved Kernel Density Estimation Method for Identifying Disease Clusters.” *Journal of Geographical Systems* 14 (3): 243–64. https://doi.org/10.1007/s10109-010-0146-0.

Carter-Pokras, Olivia, and Claudia Baquet. 2002. “What Is a ‘Health Disparity’?” *Public Health Reports* 117 (January 2000): 426–34. https://doi.org/10.1093/phr/117.5.426.

Cecen, Emre, Dilek Gunes, Kamer Mutafoglu, Faik Sarialioglu, and Nur Olgun. 2011. “The Time to Diagnosis in Childhood Lymphomas and Other Solid Tumors.” *Pediatric Blood & Cancer* 57 (3): 392–97. https://doi.org/10.1002/pbc.23072.

Chaix, Basile, Maria Rosvall, and Juan Merlo. 2007. “Recent Increase of Neighborhood Socioeconomic Effects on Ischemic Heart Disease Mortality: A Multilevel Survival Analysis of Two Large Swedish Cohorts.” *American Journal of Epidemiology* 165 (1): 22–26. https://doi.org/10.1093/aje/kwj322.

Chen, Zhi, Leslie Robison, Roger Giller, Mark Krailo, Mary Davis, Stella Davies, and Xiao Ou Shu. 2006. “Environmental Exposure to Residential Pesticides, Chemicals, Dusts, Fumes, and Metals, and Risk of Childhood Germ Cell Tumors.” *International Journal of Hygiene and Environmental Health* 209 (1): 31–40. https://doi.org/10.1016/j.ijheh.2005.08.001.

Clifford, Nicholas J., Sarah L. Holloway, Stephen P. Rice, and Gill Valentine. 2009. *Key Concepts in Geography*. Second Edi. London EC1Y 1SP: SAGE Publications Ltd.

Cordier, S, L Mandereau, S Preston-Martin, J Little, F Lubin, B Mueller, E Holly, et al. 2001. “Parental Occupations and Childhood Brain Tumors: Results of an International Case-Control Study.” *Cancer Causes Control* 12 (9): 865–74. http://www.ncbi.nlm.nih.gov/pubmed/11714115.

Cox, D. R. 1972. “Regression Models and Life-Tables.” *Journal of the Royal Statistical Society . Series B (Methodological)* 34 (2): 187–220. http://www.jstor.org/stable/2985181.

Cutter, Susan L., Reginald Golledge, and William L. Graf. 2002. “The Big Questions in Geography.” *The Professional Geographer* 54 (January): 305–17. https://doi.org/10.1111/0033-0124.00332.

D’Andrea, Mark A, and G Kesava Reddy. 2014. “Health Effects of Benzene Exposure among Children Following a Flaring Incident at the British Petroleum Refinery in Texas City.” *Pediatric Hematology and Oncology* 31 (1): 1–10. https://doi.org/10.3109/08880018.2013.831511.

Dai, Jian, Zhongmin Li, and David Rocke. 2006. “Hierarchical Logistic Regression Modeling with SAS GLIMMIX.” *… Proceedings of Western Users of SAS …*, 1–9. http://www.lexjansen.com/wuss/2006/analytics/ANL-Dai.pdf.

Dang-Tan, Tam, and Eduardo L. Franco. 2007. “Diagnosis Delays in Childhood Cancer: A Review.” *Cancer* 110 (4): 703–13. https://doi.org/10.1002/cncr.22849.

Dang-Tan, Tam, Helen Trottier, Leslie S. Mery, Howard I. Morrison, Ronald D. Barr, Mark L. Greenberg, and Eduardo L. Franco. 2008. “Delays in Diagnosis and Treatment Among Children and Adolescents With Cancer in Canada.” *Pediatr Blood Cancer* 2008 (51): 468–474. https://doi.org/10.1002/pbc.21600.

———. 2010. “Determinants of Delays in Treatment Initiation in Children and Adolescents Diagnosed with Leukemia or Lymphoma in Canada.” *International Journal of Cancer* 126 (8): 1936–43. https://doi.org/10.1002/ijc.24906.

Danysh, Heather E., Mitchell Laura E., Kai Zhang, Michael E. Scheurer, and Philip J. Lupo. 2015. “Traffic-Related Air Pollution and the Incidence of Childhood Central Nervous System Tumors: Texas, 2001–2009 Heather.” *Pediatr Blood Cancer* 2015 (62): 1572–78. https://doi.org/10.1002/pbc.25549.

Danysh, Heather E., Kai Zhang, Laura E. Mitchell, Michael E. Scheurer, and Philip J. Lupo. 2016. “Maternal Residential Proximity to Major Roadways at Delivery and Childhood Central Nervous System Tumors.” *Environmental Research* 146: 315–22. https://doi.org/10.1016/j.envres.2016.01.012.

Diggle, P J, and a G Chetwynd. 1991. “Second-Order Analysis of Spatial Clustering for Inhomogeneous Populations.” *Biometrics* 47 (3): 1155–63. https://doi.org/http://www.jstor.org/stable/2532668.

Dobrovoljac, Milana, Heinz Hengartner, Eugen Boltshauser, and Michael A. Grotzer. 2002. “Delay in the Diagnosis of Paediatric Brain Tumours.” *European Journal of Pediatrics* 161 (12): 663–67. https://doi.org/10.1007/s00431-002-1088-4.

Evans, N T, C E Wakefield, J K McLoone, and R J Cohn. 2014. “Familial Diagnostic Experiences in Paediatric Oncology.” *British Journal of Cancer*, no. January 2007: 1–4. https://doi.org/10.1038/bjc.2014.516.

Fajardo-Gutiérrez, Arturo, Aidé María Sandoval-Mex, Juan Manuel Mejía-Aranguré, Mario Enrique Rendón-Macías, and María Del Carmen Martínez-García. 2002. “Clinical and Social Factors That Affect the Time to Diagnosis of Mexican Children with Cancer.” *Medical and Pediatric Oncology* 39 (1): 25–31. https://doi.org/10.1002/mpo.10100.

Feller, Martin, Martin Adam, Marcel Zwahlen, Pierluigi Brazzola, Felix Niggli, and Claudia Kuehni. 2010. “Family Characteristics as Risk Factors for Childhood Acute Lymphoblastic Leukemia: A Population-Based Case-Control Study.” *PLoS ONE* 5 (10): 1–7. https://doi.org/10.1371/journal.pone.0013156.

Fluchel, Mark N., Anne C. Kirchhoff, Julia Bodson, Carol Sweeney, Sandra L. Edwards, Qian Ding, Gregory J. Stoddard, and Anita Y. Kinney. 2014. “Geography and the Burden of Care in Pediatric Cancers Mark.” *Pediatr Blood Cancer* 2014 (61): 1918–24. https://doi.org/10.1002/pbc.25170.

Fotheringham, A.S., and David W.S. Wong. 1991. “The Modifiable Areal Unit Problem in Multivariate Statistical Analysis.” *Environment and Planning A* 23 (7): 1025–44. https://doi.org/10.1068/a231025.

Fotheringham, A Stewart, and F Benjamin Zhan. 1996. “A Comparison of Three Exploratory Methods for Cluster Detection in Spatial Point Patterns.” *Geographical Analysis* 28 (3): 200–218. https://doi.org/10.1111/j.1538-4632.1996.tb00931.x.

Freeman, H P. 1989. “Cancer in the Socioeconomically Disadvantaged.” *CA: A Cancer Journal for Clinicians* 39 (5): 266–88. http://www.ncbi.nlm.nih.gov/pubmed/2513099.

Gehlert, Sarah, and Graham A. Colditz. 2011. “Cancer Disparities: Unmet Challenges in the Elimination of Disparities.” *Cancer Epidemiology Biomarkers and Prevention*. https://doi.org/10.1158/1055-9965.EPI-11-0628.

Goddard, A G, J E Kingston, and J L Hungerford. 1999. “Delay in Diagnosis of Retinoblastoma: Risk Factors and Treatment Outcome.” *The British Journal of Ophthalmology* 83 (12): 1320–23. https://doi.org/10.1136/bjo.83.12.1320.

Golledge, R.G. 2002. “The Nature of Geographic Knowledge.” *Annals of the Association of American Geographers* 92 (1): 1–14. https://doi.org/10.1111/1467-8306.00276.

Goovaerts, Pierre, Jaymie R Meliker, and Geoffrey M Jacquez. 2007. “A Comparative Analysis of Aspatial Statistics for Detecting Racial Disparities in Cancer Mortality Rates.” *International Journal of Health Geographics* 6: 32. https://doi.org/10.1186/1476-072X-6-32.

Goyal, S., J. Roscoe, W. D J Ryder, H. R. Gattamaneni, and T. O B Eden. 2004. “Symptom Interval in Young People with Bone Cancer.” *European Journal of Cancer* 40 (15): 2280–86. https://doi.org/10.1016/j.ejca.2004.05.017.

Greenop, Kathryn R., Andrea L. Hinwood, Lin Fritschi, Rodney J. Scott, John Attia, Lesley J. Ashton, John A. Heath, Bruce K. Armstrong, and Elizabeth Milne. 2015. “Vehicle Refuelling, Use of Domestic Wood Heaters and the Risk of Childhood Brain Tumours: Results From an Australian Case–Control Study.” *Pediatr Blood Cancer* 2015 (62): 229–34. https://doi.org/10.1002/pbc.

Grubb, W.R., H. J. Neboori, A. D. Diaz, H. Li, D. Kwon, and Joseph Panoff. 2016. “Racial and Ethnic Disparities in the Pediatric Hodgkin Lymphoma Population.” *Pediatr Blood Cancer* 2016 (63): 428–435. https://doi.org/10.1002/pbc.25802.

Gupta, Sumit, S. K. Morris, W. Suraweera, L. Aleksandrowicz, R. Dikshit, and P. Jha. 2016. “Childhood Cancer Mortality in India : Direct Estimates From a Nationally Representative Survey of Childhood Deaths.” *Journal of Global Oncology* JGO000935. https://doi.org/10.1200/JGO.2015.000935.

Gupta, Sumit, Rinku Sutradhar, Astrid Guttmann, Lillian Sung, and Jason D. Pole. 2014. “Socioeconomic Status and Event Free Survival in Pediatric Acute Lymphoblastic Leukemia: A Population-Based Cohort Study.” *Leukemia Research* 38 (12): 1407–12. https://doi.org/10.1016/j.leukres.2014.08.017.

Gupta, Sumit, Marta Wilejto, Jason D. Pole, Astrid Guttmann, and Lillian Sung. 2014. “Low Socioeconomic Status Is Associated with Worse Survival in Children with Cancer: A Systematic Review.” *PLoS ONE* 9 (2). https://doi.org/10.1371/journal.pone.0089482.

Haimi, M.M. 2004. “Delay in Diagnosis of Children with Cancer: A Retrospective Study of 315 Children.” *Pediatric Hematology-Oncology* 21 (1): 37–48. https://doi.org/10.1080/08880010490263579.

Halperin, Edward C., and Henry S. Friedman. 1996. “Is There a Correlation between Duration of Presenting Symptoms and Stage of Medulloblastoma at the Time of Diagnosis?” *Cancer* 78 (4): 874–80. https://doi.org/10.1002/(SICI)1097-0142(19960815)78:4<874::AID-CNCR26>3.0.CO;2-R.

Hamilton, Emma C., Hoang T. Nguyen, Yu Chia Chang, Jan M. Eberth, Janice Cormier, Linda S. Elting, and Mary T. Austin. 2016. “Health Disparities Influence Childhood Melanoma Stage at Diagnosis and Outcome.” *Journal of Pediatrics* 175 (2016): 182–87. https://doi.org/10.1016/j.jpeds.2016.04.068.

Hansen, Walter G. 1959. “How Accessibility Shapes Land Use.” *Journal of the American Planning Association* 25 (2): 73–76. https://doi.org/10.1080/01944365908978307.

Henderson, Tara O, Smita Bhatia, Navin Pinto, Wendy B London, Patrick McGrady, Catherine Crotty, Can-Lan Sun, and Susan L Cohn. 2011. “Racial and Ethnic Disparities in Risk and Survival in Children with Neuroblastoma: A Children’s Oncology Group Study.” *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 29 (1): 76–82. https://doi.org/10.1200/JCO.2010.29.6103.

Holmes, John H., Amy Lehman, Erinn Hade, Amy K. Ferketich, Sarah Gehlert, Garth H. Rauscher, Judith Abrams, and Chloe E. Bird. 2008. “Challenges for Multilevel Health Disparities Research in a Transdisciplinary Environment.” *American Journal of Preventive Medicine* 35 (2 SUPPL.): 182–92. https://doi.org/10.1016/j.amepre.2008.05.019.

Hord, Marilew H., Terry L. Smith, Steven J. Culbert, Lawrence S. Frankel, and Donald P. Pinkel. 1996. “Ethnicity and Cure Rates of Texas Children with Acute Lymphoid Leukemia.” *Cancer* 77 (3): 563–69. https://doi.org/10.1002/(SICI)1097-0142(19960201)77:3<563::AID-CNCR20>3.0.CO;2-1.

Hosmer, David W., and Stanley Lemeshaw. 2000. *Applied Logistic Regression*. *Analysis*. Second edi. Vol. 7. New York: A Wiley-Interscience Publication.

Houben, M. P W A, J. W W Coebergh, J. M. Birch, C. C. Tijssen, C. M. Van Duijn, and R. J Q McNally. 2006. “Space-Time Clustering of Glioma Cannot Be Attributed to Specific Histological Subgroups.” *European Journal of Epidemiology* 21 (3): 197–201. https://doi.org/10.1007/s10654-006-0003-0.

Howard, Scott C., Monika L. Metzger, Judith A. Wilimas, Yuri Quintana, Ching H. Pui, Leslie L. Robison, and Raul C. Ribeiro. 2008. “Childhood Cancer Epidemiology in Low-Income Countries.” *Cancer* 112 (3): 461–72. https://doi.org/10.1002/cncr.23205.

Hsieh, Michael H, Maxwell V Meng, Thomas J Walsh, Katherine K Matthay, and Laurence S Baskin. 2009. “Increasing Incidence of Neuroblastoma and Potentially Higher Associated Mortality of Children from Nonmetropolitan Areas: Analysis of the Surveillance, Epidemiology, and End Results Database.” *Journal of Pediatric Hematology/Oncology* 31 (12): 942–46. https://doi.org/10.1097/MPH.0b013e3181bcc809.

Huang, Xuelin, and Robert A. Wolfe. 2002. “A Frailty Model for Informative Censoring.” *Biometrics* 58 (3): 510–20. https://doi.org/Doi 10.2307/2289657.

Huff, D L. 2000. “Don’t Misuse the Huff Model in GIS.” *Business Geographies* 8 (8): 12.

Jemal, Ahmedin, Rebecca Siegel, Elizabeth Ward, Yongping Hao, Jiaquan Xu, Taylor Murray, and Michael J Thun. 2008. “Cancer Statistics, 2008.” *CA: A Cancer Journal for Clinicians* 58 (2): 71–96. https://doi.org/10.3322/CA.2007.0010.

Joseph, Alun E., and David R. Phillips. 1984. *Accessibility and Utilization: Geographical Perspectives on Health Care Delivery*. Harper & Row Publishers, New York, 214pp.

Kaatsch, Peter. 2010. “Epidemiology of Childhood Cancer.” *Cancer Treatment Reviews* 36 (4): 277–85. https://doi.org/10.1016/j.ctrv.2010.02.003.

Kadan-Lottick, Nina S, Kirsten K Ness, Smita Bhatia, and James G Gurney. 2003. “Survival Variability by Race and Ethnicity in Childhood Acute Lymphoblastic Leukemia.” *JAMA : The Journal of the American Medical Association* 290 (15): 2008–14. https://doi.org/10.1001/jama.290.15.2008.

Kaplan, E. L., and Paul Meier. 1958. “Nonparametric Estimation from Incomplete Observations.” *American Statistical Association* 53 (282): 457–81. http://www.jstor.org/stable/2281868.

Keegan, Theresa H M, Li Tao, Mindy C DeRouen, Xiao-Cheng Wu, Pinki Prasad, Charles F Lynch, Margarett Shnorhavorian, et al. 2014. “Medical Care in Adolescents and Young Adult Cancer Survivors: What Are the Biggest Access-Related Barriers?” *Journal of Cancer Survivorship : Research and Practice* 8 (2): 282–92. https://doi.org/10.1007/s11764-013-0332-4.

Kent, Erin E., Leonard S. Sender, Joan A. Largent, and Hoda Anton-Culver. 2009. “Leukemia Survival in Children, Adolescents, and Young Adults: Influence of Socioeconomic Status and Other Demographic Factors.” *Cancer Causes & Control : CCC* 20 (8): 1409–20. https://doi.org/10.1007/s10552-009-9367-2.

Keppel, Kenneth, Elsie Pamuk, John Lynch, Olivia Carter-Pokras, Insun Kim, Vickie Mays, Jeffrey Pearcy, Victor Schoenbach, and Joel S Weissman. 2005. “Methodological Issues in Measuring Health Disparities.” *Vital Health Stat* 2 (2141): 1–16. https://doi.org/10.1016/j.micinf.2011.07.011.Innate.

Kirchhoff, Anne C, Holly L Spraker-Perlman, Molly McFadden, Echo L Warner, Kevin C Oeffinger, Jennifer Wright, and Anita Y Kinney. 2014. “Sociodemographic Disparities in Quality of Life for Survivors of Adolescent and Young Adult Cancers in the Behavioral Risk Factor Surveillance System.” *Journal of Adolescent and Young Adult Oncology* 3 (2): 66–74. https://doi.org/10.1089/jayao.2013.0035.

Klein-Geltink, Julia E., Lisa M. Pogany, Ronald D. Barr, Mark L. Greenberg, and Leslie S. Mery. 2005. “Waiting Times for Cancer Care in Canadian Children: Impact of Distance, Clinical, and Demographic Factors.” *Pediatric Blood and Cancer* 44 (4): 318–27. https://doi.org/10.1002/pbc.20156.

Klein, John P., and Melvin L. Moeschberger. 2003. *SURVIVAL ANALYSIS Techniques for Censored and Truncated Data*. Second Edi. New York: Springer-Verlag New York, Inc.

Kleinbaum, D G, L L Kupper, A Nizam, and K E Muller. 2008. *Applied Regression Analysis and Other Multivariable Methods*. Fouth Edit. Duxbury Press/Cengage Learning, Pacific Grove.

Kleinschmidt, I, B L Sharp, G P Y Clarke, B Curtis, and C Fraser. 2001. “Use of Generalized Linear Mixed Models in the Spatial Analysis of Small-Area Malaria Incidence Rates in KwaZulu Natal, South Africa.” *Am J Epidemiol* 153 (12). https://doi.org/10.1093/aje/153.12.1213.

Knoble, Naomi B., Melissa A. Alderfer, and Md Jobayer Hossain. 2016. “Socioeconomic Status (SES) and Childhood Acute Myeloid Leukemia (AML) Mortality Risk: Analysis of SEER Data.” *Cancer Epidemiology* 44: 101–8. https://doi.org/10.1016/j.canep.2016.07.007.

Krieger, Nancy. 2005. “Defining and Investigating Social Disparities in Cancer: Critical Issues.” *Cancer Causes and Control* 16 (1): 5–14. https://doi.org/10.1007/s10552-004-1251-5.

Kulldorff, Martin. 1998. “Statistical Methods for Spatial Epidemiology: Tests for Randomness.” *GIS and Health*, no. January 1998: 68–82. http://site.ebrary.com.ezproxy1.lib.asu.edu/lib/asulib/docDetail.action?docID=10054949.

Kulldorff, Martin, Richard Heffernan, Jessica Hartman, Renato Assuncao, and Farzad Mostashari. 2005. “A Space-Time Permutation Scan Statistic for Disease Outbreak Detection.” *PLoS Medicine* 2 (3): 0216–24. https://doi.org/10.1371/journal.pmed.0020059.

Kulldorff, Martin, Lan Huang, and Kevin Konty. 2009. “A Scan Statistic for Continuous Data Based on the Normal Probability Model.” *International Journal of Health Geographics* 8 (1): 58. https://doi.org/10.1186/1476-072X-8-58.

Lin, Yan, Mario Schootman, and F. Benjamin Zhan. 2015. “Racial/Ethnic, Area Socioeconomic, and Geographic Disparities of Cervical Cancer Survival in Texas.” *Applied Geography* 56: 21–28. https://doi.org/10.1016/j.apgeog.2014.10.004.

Liu, Lei, and Xuelin Huang. 2008. “The Use of Gaussian Quadrature for Estimation in Frailty Proportional Hazardsmodels.” *Statistics in Medicine* 27 (14): 2665–83. https://doi.org/10.1002/sim.3077.

Luo, Wei, and Yi Qi. 2009. “An Enhanced Two-Step Floating Catchment Area (E2SFCA) Method for Measuring Spatial Accessibility to Primary Care Physicians.” *Health and Place* 15 (4): 1100–1107. https://doi.org/10.1016/j.healthplace.2009.06.002.

Luo, Wei, and Fahui Wang. 2003. “Measures of Spatial Accessibility to Health Care in a GIS Environment: Synthesis and a Case Study in the Chicago Region.” *Environment and Planning B: Planning and Design* 30 (6): 865–84. https://doi.org/10.1068/b29120.

Martin, Sean, Corinne Ulrich, Mark Munsell, Sarah Taylor, Georgia Lange, and Archie Bleyer. 2007. “Delays in Cancer Diagnosis in Underinsured Young Adults and Older Adolescents.” *The Oncologist* 12 (7): 816–24. https://doi.org/10.1634/theoncologist.12-7-816.

McGrail, Matthew R., and John S. Humphreys. 2009. “Measuring Spatial Accessibility to Primary Care in Rural Areas: Improving the Effectiveness of the Two-Step Floating Catchment Area Method.” *Applied Geography* 29 (4): 533–41. https://doi.org/10.1016/j.apgeog.2008.12.003.

McNally, Richard J.Q., Judith Rankin, Mark D.F. Shirley, Stephen P. Rushton, and Tanja Pless-Mulloli. 2008. “Space-Time Analysis of Down Syndrome: Results Consistent with Transient Pre-Disposing Contagious Agent.” *International Journal of Epidemiology* 37 (5): 1169–79. https://doi.org/10.1093/ije/dyn083.

Mehta, Vivek, Ann Chapman, P. Daniel McNeely, Simon Walling, William J. Howes, Leslie N. Sutton, James T. Rutka, Timothy B. Mapstone, and Paul Steinbok. 2002. “Latency between Symptom Onset and Diagnosis of Pediatric Brain Tumors: An Eastern Canadian Geographic Study.” *Neurosurgery* 51 (2): 365–73. https://doi.org/10.1097/00006123-200208000-00012.

Metzger, Monika L, Sharon M Castellino, Melissa M Hudson, Shesh N Rai, Sue C Kaste, Matthew J Krasin, Larry E Kun, Ching-Hon Pui, and Scott C Howard. 2008. “Effect of Race on the Outcome of Pediatric Patients with Hodgkin’s Lymphoma.” *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 26 (8): 1282–88. https://doi.org/10.1200/JCO.2007.14.0699.

Moran, P. A. P. 1950. “Notes on Continuous Stochastic Phenomena.” *Biometrika* 37 (1): 17–23. http://www.jstor.org/stable/2332142.

Murphy, Melissa M., Jennifer F. Tseng, and Shimul A. Shah. 2010. “Disparities in Cancer Care: An Operative Perspective.” *Surgery* 147 (5): 733–37. https://doi.org/10.1016/j.surg.2009.10.050.

National Institutes of Health. 1979. “The Belmont Report.” *The Belmont Report Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, 4–6. https://doi.org/10.1002/9780471462422.eoct093.

———. 2009. “NIH Health Disparities Strategic Plan and Budget Fiscal Years 2009-2013.” https://www.nimhd.nih.gov/docs/2009-2013nih_health_disparities_strategic_plan_and_budget.pdf.

Okcu, Mehmet Fatih, Karen J. Goodman, Susan E. Carozza, Nancy S. Weiss, Keith D. Burau, W. Archie Bleyer, and Sharon P. Cooper. 2002. “Birth Weight, Ethnicity, and Occurrence of Cancer in Children: A Population-Based, Incident Case-Control Study in the State of Texas, USA.” *Cancer Causes and Control* 13 (7): 595–602. https://doi.org/10.1023/A:1019555912243.

Openshaw, Stan, Martin Charlton, Colin Wymer, and Alan Craft. 1987. “A Mark 1 Geographical Analysis Machine for the Automated Analysis of Point Data Sets.” *International Journal of Geographical Information Systems* 1 (4): 335–58. https://doi.org/10.1080/02693798708927821.

Ord, J. K., and Arthur Getis. 1995. “Local Spatial Autocorrelation Statistics: Distributional Issues and an Application.” *Geographical Analysis* 27 (4): 286–306. https://doi.org/10.1111/j.1538-4632.1995.tb00912.x.

Pagaoa, Melissa A., M. Fatih Okcu, Melissa L. Bondy, and Michael E. Scheurer. 2011. “Associations between Vaccination and Childhood Cancers in Texas Regions.” *Journal of Pediatrics* 158 (6): 996–1002. https://doi.org/10.1016/j.jpeds.2010.11.054.

Park, Elyse R, Frederick P Li, Yan Liu, Karen M Emmons, Arthur Ablin, Leslie L Robison, and Ann C Mertens. 2005. “Health Insurance Coverage in Survivors of Childhood Cancer: The Childhood Cancer Survivor Study.” *J Clin Oncol* 23 (36): 9187–97. https://doi.org/10.1200/JCO.2005.01.7418.

Patel, Sunita K., Nathaniel Fernandez, Noya Dekel, Anne Turk, Adrienne Meier, Paula Ross, and Joseph Rosenthal. 2016. “Socioeconomic Status as a Possible Moderator of Neurocognitive Outcomes in Children with Cancer.” *Psycho-Oncology* 25 (1): 115–18. https://doi.org/10.1002/pon.3797.

Pattison, William D. 1990. “The Four Traditions of Geography.” *Journal of Geography* 89 (5): 202–6. https://doi.org/10.1080/00221349008979196.

Peckham, Erin, Michael Scheurer, Heather Danysh, Joseph Lubega, Peter Langlois, and Philip Lupo. 2015. “Residential Radon Exposure and Incidence of Childhood Lymphoma in Texas, 1995–2011.” *International Journal of Environmental Research and Public Health* 12 (10): 12110–26. https://doi.org/10.3390/ijerph121012110.

Piwkham, Duangjai, Jonathan A L Gelfond, Budsaba Rerkamnuaychoke, Samart Pakakasama, Vivienne I. Rebel, Brad H. Pollock, Naomi J. Winick, Anderson B. Collier, Gail E. Tomlinson, and Joke Beuten. 2011. “Multilocus Association of Genetic Variants in MLL, CREBBP, EP300, and TOP2A with Childhood Acute Lymphoblastic Leukemia in Hispanics from Texas.” *Cancer Epidemiology Biomarkers and Prevention* 20 (6): 1204–12. https://doi.org/10.1158/1055-9965.EPI-11-0059.

Polite, Blase N., Lucile L. Adams-Campbell, Otis W. Brawley, Nina Bickell, John M. Carethers, Christopher R. Flowers, Margaret Foti, et al. 2017. “Charting the Future of Cancer Health Disparities Research: A Position Statement From the American Association for Cancer Research, the American Cancer Society, the American Society of Clinical Oncology, and the National Cancer Institute.” *Journal of Clinical Oncology* 67 (5): JCO.2017.73.654. https://doi.org/10.1200/JCO.2017.73.6546.

Pollock, B H, M R DeBaun, B M Camitta, J J Shuster, Y Ravindranath, D J Pullen, V J Land, D H Mahoney, S J Lauer, and S B Murphy. 2000. “Racial Differences in the Survival of Childhood B-Precursor Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Study.” *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 18 (4): 813–23. http://www.ncbi.nlm.nih.gov/pubmed/10673523.

Pollock, Brad H., Jeffrey P. Krischer, and Teresa J. Vietti. 1991. “Interval between Symptom Onset and Diagnosis of Pediatric Solid Tumors.” *The Journal of Pediatrics* 119 (5): 725–32. https://doi.org/10.1016/S0022-3476(05)80287-2.

Potthoff, R. F., and Maurice Whittinghill. 1966. “Testing for Homogeneity.” *Biometrika* 53 (1): 183–90.

Pui, Ching Hon, Deqing Pei, Alberto S. Pappo, Scott C. Howard, Cheng Cheng, John T. Sandlund, Wayne L. Furman, et al. 2012. “Treatment Outcomes in Black and White Children with Cancer: Results from the Seer Database and St. Jude Children’s Research Hospital, 1992 through 2007.” *Journal of Clinical Oncology* 30 (16): 2005–12. https://doi.org/10.1200/JCO.2011.40.8617.

R Core, Team. 2013. *R: A Language and Environment for Statistical Computing.* R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/.

Radke, John, and Lan Mu. 2000. “Spatial Decompositions, Modeling and Mapping Service Regions to Predict Access to Social Programs.” *Geographic Information Sciences* 6 (2): 105–12. https://doi.org/10.1080/10824000009480538.

Ramírez-Ortiz, Marco A., M. Veronica Ponce-Castañeda, M. Lourdes Cabrera-Muñoz, Aurora Medina-Sansón, Xinhua Liu, and Manuela A. Orjuela. 2014. “Diagnostic Delay and Sociodemographic Predictors of Stage at Diagnosis and Mortality in Unilateral and Bilateral Retinoblastoma.” *Cancer Epidemiology Biomarkers and Prevention* 23 (5): 784–92. https://doi.org/10.1158/1055-9965.EPI-13-1069.

Read, Jen’nan Ghazal, and Michael O. Emerson. 2005. “Racial Context, Black Immigration and the U .S. Black/White Health Disparity.” *Social Forces* 84 (1): 181–99. https://doi.org/10.1353/sof.2005.0120.

Reulecke, B. C., C. G. Erker, B. J. Fiedler, T.-U. Niederstadt, and G. Kurlemann. 2007. “Brain Tumors in Children: Initial Symptoms and Their Influence on the Time Span Between Symptom Onset and Diagnosis.” *Journal of Child Neurology* 23 (2): 178–83. https://doi.org/10.1177/0883073807308692.

Reynolds, Peggy, Julie Von Behren, Robert B. Gunier, Debbie E. Goldberg, Martha Harnly, and Andrew Hertz. 2005. “Agricultural Pesticide Use and Childhood Cancer in California.” *Epidemiology (Cambridge, Mass.)* 16 (1): 93–100. https://doi.org/10.1097/01.ede.0000147119.32704.5c.

Ries, L. a. G., M. a. Smith, J. G. Gurney, M. Linet, T. Tamra, J. L. Young, and G. R. Bunin. 1999. “Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995.” *NIH Pub. No. 99-4649*, 179 pp.

Rodrigues, Karla E S, Maria do Rosário D O Latorre, and Beatriz de Camargo. 2004. “[Delayed Diagnosis in Retinoblastoma].” *Jornal de Pediatria* 80 (6): 511–16. http://www.jped.com.br/conteudo/04-80-06-511/ing.asp.

Rogerson, Peter A. 2001. “A Statistical Method for the Detection of Geographic Clustering.” *Geographical Analysis,* 33 (3): 215–227. https://doi.org/10.1111/j.1538-4632.2001.tb00445.x.

Rosenblatt, R A, and D M Lishner. 1991. “Surplus or Shortage? Unraveling the Physician Supply Conundrum.” *The Western Journal of Medicine* 154 (1): 43–50. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1002675&tool=pmcentrez&rendertype=abstract.

Rushton, G, and P Lolonis. 1996. “Exploratory Spatial Analysis of Birth Defect Rates in an Urban Population.” *Statistics in Medicine* 15 (7–9): 717–26. https://doi.org/10.1002/(SICI)1097-0258(19960415)15:7/9<717::AID-SIM243>3.0.CO;2-0.

Rushton, Gerard, Gregory Elmes, and Robert Mcmaster. 1999. “Considerations for Improving Geographic Information System Research in Public Health,” no. CDC: 31–49.

Ryn, Michelle Van. 2002. “Research on the Provider Contribution to Race / Ethnicity Disparities in Medical Care Author (s): Michelle van Ryn Source : Medical Care , Vol . 40 , No . 1 , Supplement : Racial-Disparities Research in Veterans Health Care Administration (Jan ., 2002.” *MEDICAL CARE* 40 (1): 1–140--1–151. http://www.jstor.org/stable/3767871.

Saha, V, S Love, T Eden, P Micallef-Eynaud, and G MacKinlay. 1993. “Determinants of Symptom Interval in Childhood Cancer.” *Archives of Disease in Childhood* 68 (6): 771–74. https://doi.org/10.1136/adc.68.6.771.

Schootman, Mario, Donna B. Jeffe, Min Lian, William E. Gillanders, and Rebecca Aft. 2009. “The Role of Poverty Rate and Racial Distribution in the Geographic Clustering of Breast Cancer Survival among Older Women: A Geographic and Multilevel Analysis.” *American Journal of Epidemiology* 169 (5): 554–61. https://doi.org/10.1093/aje/kwn369.

Senkayi, Sala N., Melanie L. Sattler, Nancy Rowe, and Victoria C.P. Chen. 2014. “Investigation of an Association between Childhood Leukemia Incidences and Airports in Texas.” *Atmospheric Pollution Research* 5 (2): 189–95. https://doi.org/10.5094/APR.2014.023.

Short, Margaret, Bradley P Carlin, and Sally Bushhouse. 2016. “Using Hierarchical Spatial Models for Cancer Control Planning in Minnesota (United States) Author (s): Margaret Short , Bradley P . Carlin and Sally Bushhouse Published by : Springer Stable URL : Http://Www.Jstor.Org/Stable/3554027 REFERENCES Linked R.” *Cancer Causes and Control* 13 (10): 903–16.

Siegel, Rebecca L., Kimberly D. Miller, and Ahmedin Jemal. 2018. “Cancer Statistics, 2018.” *CA: A Cancer Journal for Clinicians* 68 (1): 7–30. https://doi.org/10.3322/caac.21442.

Skyrud, Katrine Damgaard, Freddie Bray, and Bjørn Møller. 2014. “A Comparison of Relative and Cause-Specific Survival by Cancer Site, Age and Time since Diagnosis.” *International Journal of Cancer* 135 (1): 196–203. https://doi.org/10.1002/ijc.28645.

Smedley, Brian D, Adrienne Y Stith, and Alan R Nelson. 2003. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care.* http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2003-02632-000&site=ehost-live.

Stefan, Daniela Cristina, and Femke Siemonsma. 2011. “Delay and Causes of Delay in the Diagnosis of Childhood Cancer in Africa.” *Pediatric Blood and Cancer* 56 (1): 80–85. https://doi.org/10.1002/pbc.22714.

Steinberg, Michael L. 2008. “Inequity in Cancer Care: Explanations and Solutions for Disparity.” *Seminars in Radiation Oncology* 18 (3): 161–67. https://doi.org/10.1016/j.semradonc.2008.01.003.

Stewart, B, C. P. Wild (eds.), and WHO International Agency for Research on Cancer. 2014. “World Cancer Report 2014 [Online].” http://www.thehealthwell.info/node/725845.

Stiller, Charles A. 2004. “Epidemiology and Genetics of Childhood Cancer.” *Oncogene* 23 (38): 6429–44. https://doi.org/10.1038/sj.onc.1207717.

Talbot, T O, M Kulldorff, S P Forand, and V B Haley. 2000. “Evaluation of Spatial Filters to Create Smoothed Maps of Health Data.” *Statistics in Medicine* 19: 2399–2408. https://doi.org/10.1002/1097-0258(20000915/30)19:17/18<2399::AID-SIM577>3.0.CO;2-R.

Tango, Toshiro. 1995. “A Class of Tests for Detecting ‘General’ and ‘Focused’ Clustering of Rare Diseases.” *Statistics in Medicine* 14 (21–22): 2323–34. https://doi.org/10.1002/sim.4780142105.

Theophilides, Constandinos N., Sean C. Ahearn, Sue Grady, and Mario Merlino. 2003. “Identifying West Nile Virus Risk Areas: The Dynamic Continuous-Area Space-Time System.” *American Journal of Epidemiology* 157 (9): 843–54. https://doi.org/10.1093/aje/kwg046.

Thompson, James A., Susan E. Carozza, Wesley T. Bissett, and Li Zhu. 2010. “Risks of Childhood Cancer among Texas Watersheds, Based on Mothers’ Living Locations at the Time of Birth.” *Journal of Water and Health* 8 (1): 139–46. https://doi.org/10.2166/wh.2009.018.

Thompson, James A., Susan E. Carozza, and Li Zhu. 2007. “An Evaluation of Spatial and Multivariate Covariance among Childhood Cancer Histotypes in Texas (United States).” *Cancer Causes and Control* 18 (1): 105–13. https://doi.org/10.1007/s10552-006-0085-8.

Thompson, James A, Susan E Carozza, and Li Zhu. 2008. “Geographic Risk Modeling of Childhood Cancer Relative to County-Level Crops, Hazardous Air Pollutants and Population Density Characteristics in Texas.” *Environmental Health : A Global Access Science Source* 7 (1): 45. https://doi.org/10.1186/1476-069X-7-45.

Tian, Nancy, Pierre Goovaerts, F Benjamin Zhan, and Jeff G Wilson. 2010. “Identification of Racial Disparities in Breast Cancer Mortality: Does Scale Matter?” *International Journal of Health Geographics* 9: 35. https://doi.org/10.1186/1476-072X-9-35.

Tian, Nancy, J Gaines Wilson, and F Benjamin Zhan. 2011. “Spatial Association of Racial/Ethnic Disparities between Late-Stage Diagnosis and Mortality for Female Breast Cancer: Where to Intervene?” *International Journal of Health Geographics* 10 (1): 24. https://doi.org/10.1186/1476-072X-10-24.

Torre, Lindsey A., Freddie Bray, Rebecca L. Siegel, Jacques Ferlay, Joannie Lortet-tieulent, and Ahmedin Jemal. 2015. “Global Cancer Statistics, 2012.” *CA: A Cancer Journal of Clinicians.* 65 (2): 87–108. https://doi.org/10.3322/caac.21262.

Turner, B. L. 2002. “Contested Identities: Human-Environment Geography and Disciplinary Implications in a Restructuring Academy.” *Annals of the Association of American Geographers* 92 (1): 52–74. https://doi.org/10.1111/1467-8306.00279.

Urdan, Timothy C. 2017. *Statistics in Plain English*. *Routledge: Taylor & Francis Group*. Fourth Edi. New York, NY.

US Department of Health and Human Services. 2000. “Healthy People 2010: Understanding and Improving Health.” Washington, DC: U.S. Government Printing Office, November 2000.

———. 2008. “The Secretary’s Advisory Committee on National Health Promotion and Disease Prevention Objectives for 2020. Phase I Report: Recommendations for the Framework and Format of Healthy People 2020.” *Section IV: Advisory Committee Findings and Recommendations*, 1–91.

Wallach, Marjorie, Aubin Balmer, Francis Munier, Susan Houghton, Sandro Pampallona, Nicolas von der Weid, and Maja Beck-Popovic. 2006. “Shorter Time to Diagnosis and Improved Stage at Presentation in Swiss Patients with Retinoblastoma Treated from 1963 to 2004.” *Pediatrics* 118 (5): e1493–98. https://doi.org/10.1542/peds.2006-0784.

Wan, Neng, F. Benjamin Zhan, Yongmei Lu, and John P. Tiefenbacher. 2012a. “Access to Healthcare and Disparities in Colorectal Cancer Survival in Texas.” *Health and Place* 18 (2): 321–29. https://doi.org/10.1016/j.healthplace.2011.10.007.

———. 2012b. “Access to Healthcare and Disparities in Colorectal Cancer Survival in Texas.” *Health and Place* 18 (2): 321–29. https://doi.org/10.1016/j.healthplace.2011.10.007.

Wan, Neng, F. Benjamin Zhan, Bin Zou, and Edwin Chow. 2012. “A Relative Spatial Access Assessment Approach for Analyzing Potential Spatial Access to Colorectal Cancer Services in Texas.” *Applied Geography* 32 (2): 291–99. https://doi.org/10.1016/j.apgeog.2011.05.001.

Wan, Neng, F. Benjamin Zhan, Bin Zou, and J. Gaines Wilson. 2013. “Spatial Access to Health Care Services and Disparities in Colorectal Cancer Stage at Diagnosis in Texas.” *The Professional Geographer* 65 (3): 527–41. https://doi.org/10.1080/00330124.2012.700502.

Wang, Lu, and Deborah Roisman. 2011. “Modeling Spatial Accessibility of Immigrants to Culturally Diverse Family Physicians.” *Professional Geographer* 63 (1): 73–91. https://doi.org/10.1080/00330124.2010.510087.

Ward, Elizabeth, Carol Desantis, Anthony Robbins, Betsy Kohler, and Ahmedin Jemal. 2014. “Childhood and Adolescent Cancer Statistics , 2014.” *Ca Cancer J Clin* 64 (2): 83–103. https://doi.org/10.3322/caac.21219.

Ward, Elizabeth, Ahmedin Jemal, Vilma Cokkinides, Gopal K Singh, Cheryll Cardinez, Asma Ghafoor, and Michael Thun. 2010. “Cancer Disparities by Race/Ethnicity and Socioeconomic Status.” *CA: A Cancer Journal for Clinicians* 54 (2): 78–93. https://doi.org/10.3322/canjclin.54.2.78, 10.3322/canjclin.54.2.78.

Warner, Echo L, Roberto E. Montenegro, Antoinette Stroup, Anita Y. Kinney, and Anne C. Kirchhoff. 2014. “Health Care Concerns of Rural Childhood Cancer Survivors.” *Journal of Health Care for the Poor and Underserved* 25 (2): 901–12. https://doi.org/10.1353/hpu.2014.0095.

Weibull, Jörgen W. 1976. “An Axiomatic Approach to the Measurement of Accessibility.” *Regional Science and Urban Economics* 6 (4): 357–79. https://doi.org/10.1016/0166-0462(76)90031-4.

Whitehead, M, Michael Marmot, Jessica J. Allen, Orielle Solar, Alec Irwin, W L Roper, E L Baker, et al. 1992. “The Concepts and Principles of Equity and Health.” *International Journal of Health Services : Planning, Administration, Evaluation* 22 (3): 429–45. https://doi.org/10.1093/heapro/6.3.217.

Whitworth, Kristina W., Elaine Symanski, and Ann L. Coker. 2008. “Childhood Lymphohematopoietic Cancer Incidence and Hazardous Air Pollutants in Southeast Texas, 1995-2004.” *Environmental Health Perspectives* 116 (11): 1576–80. https://doi.org/10.1289/ehp.11593.

Yang, Duck Hye, Robert Goerge, and Ross Mullner. 2006. “Comparing GIS-Based Methods of Measuring Spatial Accessibility to Health Services.” *Journal of Medical Systems* 30 (1): 23–32. https://doi.org/10.1007/s10916-006-7400-5.